

LUNG CANCER IASLC NEWS

INTERNATIONAL ASSOCIATION FOR THE STUDY OF LUNG CANCER

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EVOLVING STANDARDS OF CARE

Accessing Lung Cancer Experts from Anywhere in the World

Those in search of an expert opinion can gain access through remote second-opinion programs.

People diagnosed with lung cancer do not have to live close to a major cancer center to get a second opinion from one of its experts, thanks to a growing number of remote second-opinion (RSO) programs.

“What is offered in remote second-opinion programs can vary, but the one commonality is that the patient is interacting with a physician without physically being in the same room as them,”

explained D. Ross Camidge, MD, PhD, the Joyce Zeff Endowed Chair in Lung Cancer Research at the University of Colorado School of Medicine.

Data on the frequency of patient-driven second opinions in oncology are variable, with a recent review reporting ranges from 1% to 88%. Among the motivations for seeking a second opinion are perceived need for certainty, a lack of

trust, dissatisfaction with communication, and/or a need for more personalized information.¹

Personalized Expertise

RSOs provide patients with an opportunity for an expert in the disease to review the patient's medical records, scan their lab results, and consult about the best treatment options, explained Janet Freeman-Daily, a lung cancer patient advocate and survivor.

“As lung cancer gets divided into smaller and smaller subsets by genomic drivers or other characterizations, some patients are realizing that their doctors may not be as familiar with their particular type of lung cancer, or the drugs used to treat it,” Ms. Freeman-Daily said. “With remote second opinions, you get that expert advice without having to travel.”

For example, one of the genomic drivers of lung cancer discovered in recent years is the *EML4-ALK* fusion

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EVOLVING STANDARDS OF CARE

Clinical Utility of Plasma Next-Generation Sequencing in Advanced NSCLC: Are We Ready for a ‘Blood-First’ Approach?

By Christian Rolfo, MD, PhD, MBA, Dr.h.c., and Lori Alexander, MTPW, ELS, MWC

Targeted therapy has become the standard of care in patients with advanced NSCLC and oncogenic drivers, and tissue biopsy has emerged as the gold standard in the molecular diagnosis of the disease. Guidelines recommend that all patients with newly diagnosed advanced NSCLC have molecular testing to detect five to eight predictive biomarker mutations,¹⁻³ and as the number of targetable oncogenic alterations in NSCLC continues to grow, multiplexed genetic sequencing panels are preferable over sequential or multiple single-gene tests.² However, in most patients, lung cancer is diagnosed on the basis

of small tissue biopsy or cytologic samples; consequently, complete molecular testing is not achieved in a substantial proportion of cases. Studies have shown that the use of molecular testing varies widely across practices around the world^{4,5} and that complete genotyping is carried out in approximately 8% of patients with newly diagnosed advanced NSCLC in the United States.⁶

Over the past few years, liquid biopsy has generated great interest as a minimally invasive diagnostic assay to overcome the challenges of tissue biopsy and thus increase the number of patients who can be tested for druggable biomarkers and can receive appropriate treatment based on complete molecu-

lar information. In addition, the time to the start of treatment is delayed by a long turnaround time between receipt of a tissue sample and reporting of relevant results; this delay has often led to

the initiation of chemotherapy before genomic results are available to avoid substantial deterioration in the patient's clinical condition.^{4,6,7} Liquid biopsy holds promise as a viable alternative to tissue biopsy and has been evaluated for multiple potential clinical uses, including biomarker identification, patient selection for treatment, early cancer detection, and drug resistance monitoring.

LIQUID BIOPSY EXPERT VOICES

Guidelines Related to Liquid Biopsy

EGFR testing on cell-free DNA (cfDNA) is currently recommended in the IASLC/College of American Pathologists (CAP)/Association for Molecular Pathology (AMP) guidelines for patients with limited and/or insufficient tumor tissue for molecular testing; it has also been recommended to identify *EGFR* T790M mutations in *EGFR*-mutated NSCLC progressing after treatment with first- or second-generation *EGFR* tyrosine kinase inhibitors. Testing of a tumor sample is recommended if the results of liquid biopsy are negative.² An increasing number of next-generation sequencing (NGS) platforms have been recently

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CONQUERING THORACIC CANCERS WORLDWIDE

Accessing Lung Experts Worldwide

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gene. *ALK* gene rearrangements are found in approximately 5% of NSCLCs. Historically, before the modern era of targeted therapy and checkpoint inhibition, the 5-year survival rate of patients with stage IV NSCLC is approximately 1%, with a median survival of approximately 8 months³; however, one recent study showed that patients with stage IV *ALK*-positive NSCLC given appropriate treatment had a median survival longer than 6 years.⁴

Dr. Camidge was a researcher on that study and is considered one of the world's foremost *ALK*-positive lung cancer experts. The RSO program at University of Colorado launched in December 2011 with the idea that Dr. Camidge could provide remote consults to patients with *ALK*-positive disease, avoiding the need to travel to Colorado, pay for accommodations, or take time away from work or family.

Since that time, the program has provided more than 300 RSOs to patients in 33 states and 20 countries including Bulgaria, Egypt, New Zealand, Sweden, and Uruguay. But what really sets their program apart is that Dr. Camidge does RSOs by speaking to the person via phone.

"I get to establish a relationship, and the patient can ask questions," Dr. Camidge said. "A paper [consultation] can provide facts, but part of the reason a lot of people are seeking a second opinion is that they feel something is missing. Sometimes that is expertise, and sometimes it is communication; to correct that, I think phone consultations work better."

Although Dr. Camidge said that approximately 20% of his RSOs become full-time patients, he feels that in addition to providing expertise, his job is to improve or repair the communication between the patient and their primary oncologist.

"The last line of the written opinion always says to please show [the opinion] to their treating physician to get their thoughts on the matter," Dr. Camidge explained. "Many times these opinions are just one-offs; I confirm that their oncologist is doing all the right things, and the confidence level of the patients goes up."

In some cases, though, a RSO can change the course of a patient's treatment,

according to Russell Kenneth Hales, MD, director of the thoracic oncology multidisciplinary program at the Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins.

"We certainly have patients from an outside facility [for whom] our pathologist will find something different and we are able to target a different molecular pathway," Dr. Hales said.

At Johns Hopkins, the RSO program involves patients sending in their medical records for review and an expert at Johns Hopkins sending back a written recommendation. Although Dr. Hales could not rule out RSOs ever including a phone call, he said that he has never participated in that type of RSO model.

Availability and Access

Other major cancer centers also offer RSO programs. For example, the Dana Farber Cancer Institute's Online Second Opinion program provides access to its expert oncologists to patients around the country and around the world without traveling to Boston. The program can be accessed via phone or internet, and the entire process is conducted online, including the collection of medical records. After collecting records, patients receive a written response from a physician specifically matched to accommodate the patient's needs.

The Cleveland Clinic Taussig Cancer Center also offers RSOs from its thoracic oncology department through a program called MyConsult. Patients seeking a second opinion get a written response from one doctor who specializes in the field, as well as one round of written follow-up questions and answers.

"The oncologist in the USA [who provided the second opinion] told us on the phone through a translator (a native-born Italian oncologist) that he thought my wife's brain MRI showed a possible metastasis instead of just a cyst. Because of this, my wife had successful cyberknife treatment that eliminated the spot and avoided a much more risky treatment option."

—Spouse of a patient with *ROS1* NSCLC, Italy

However, remote access to cancer experts at major institutions is by no means standard in the United States. Many major cancer centers, such as those at the Seattle Cancer Care Alliance (Fred Hutchinson Cancer Research Center),

Insurance Coverage of Remote Second Opinions

The *IASLC Lung Cancer News* recently reached out to several major U.S. healthcare insurance providers to inquire about the coverage of remote second opinions. A trend emerged: most of those contacted provided a second-opinion service to its members through a partnership company or third-party vendor. Through these programs, patients can access remote second opinions from an expert, but may not be able to select a specific physician.

Cigna offers a second opinion service to patients through its Rare Conditions Care Value (RCCV) Program, according to a company representative. Launched at the beginning of 2019, the program provides members with a plan enrolled in RCCV with free access to second opinion support service through a partnership with PinnacleCare; however, it is unclear from its website what diseases are included in this program.

Highmark—a Blue Cross Blue Shield company—offers a similar program to deliver virtual second opinions for its commercial members. In partnership with Best Doctors, Highmark members can access second opinions for rare diseases and complex cases. After a complete medical record is gathered, it is given to a Best Doctors expert, who are "clinically and academically accomplished, affiliated with a national and global centers

of excellence, and elected by their peers to the top five percent of U.S. physicians." A representative of the company said that "while it does vary some by product line, for many members this is a covered service, with no cost to the member or provider."

A representative from UnitedHealthcare said that some employers have opted to give their employees access to an individualized health education program offered through 2nd.MD. Members have access to the program at no cost share. According to its website, as part of this program, members can access "personalized consultations with medical experts by video or phone." The experts are all board-certified specialists who are practicing physicians and have led "at least 20 peer-reviewed studies in their area of specialty." ♦

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The University of Texas MD Anderson Cancer Center, and Fox Chase Cancer Center, do not offer any type of RSO.

Widespread lack of availability is not the only potential barrier to accessing RSO programs, according to Dr. Hales. The fees associated with RSOs are often not covered by insurance, forcing

patients to pay out of pocket (see Sidebar). As with all medical costs, fees for RSOs can vary from one institution to the next. The cost of an online second opinion at Dana Farber is \$2,000.⁵ The cost for a remote consult at UHealth in Colorado starts at \$785 but can increase with added services.⁶

"We are often finding that these sorts of services are more available to 'connected' patients who know to ask for them and who can afford to pay for them," Dr. Hales said. "It is unfortunate because the very

population whom this could most help are the patients who are more financially constrained who cannot afford to come see us in person."

Spreading RSOs

There has been very little downside to launching the RSO program at UHealth, according to Dr. Camidge, who said he has only ever had one complaint out of 300 patients.

*"We live in a rural area of British Columbia, and there are few [patients with *ALK* mutations] in our entire province. It was such an immense relief finally to talk with a specialist who we knew totally understood NSCLC with the *ALK* mutation, and could guide us going forward."*

—Patient, Canada

Dr. Camidge said many different people have reached out to him to "pick his brain" before launching their own RSO service.

"My advice is that this is a discerning population that does not want textbook

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Prior to initiating the RSO process, patients often must complete several forms including medical record release and legal disclaimer forms. Included in the release forms may be statements that address institutional or physician liability, for example, that the physician will not have access to important information that can be obtained from a physical examination and that the absence of this examination may affect the physician's ability to diagnose a disease.

'Blood-First' Approach from page 1

developed to not only improve the fidelity of the molecular analysis but also to increase the number of tests performed on a single specimen, allowing simultaneous evaluation of single-base variants, indels, copy number variations, and chromosomal rearrangements.⁴ However, high cost and limited availability restrict the widespread use of these platforms.

In 2018, an expert review conducted by the American Society of Clinical Oncology (ASCO) and CAP led to the conclusion that the evidence related to the use of liquid biopsy was insufficient to recommend its routine use for making treatment decisions and monitoring treatment.⁸ However, later that year, the IASLC published a statement paper to note that “liquid biopsy approaches have significant potential to improve patient care, and immediate implementation in the clinic is justified in a number of therapeutic settings relevant to NSCLC.”⁹ Several liquid biopsy assays are available for use in clinical practice, but only one is approved by the U.S. Food and Drug Administration (FDA): the cobas® EGFR Mutation Test (Roche, Basel, Switzerland) in NSCLC.¹⁰

Head-to-Head Comparison of Liquid and Tissue Biopsy

One issue of concern with liquid biopsy testing is how its results compare with those of tissue biopsy. Among the most recent studies in this area is the multicenter prospective Noninvasive versus Invasive Lung Evaluation (NILE) trial, which was conducted to determine whether a validated and highly sensitive plasma NGS test (Guardant360; Guardant Health, Redwood City) used at the time of diagnosis of NSCLC could prove non-inferior to standard-of-care tissue genotyping in identifying guideline-

Table 1. Comparison of Plasma and Tissue Genotyping in NILE Trial

Outcome	Source for Genotyping (N = 282)	
	Plasma	Tissue
Guideline-recommended biomarker identified	27.3%	21.3%
Guideline-complete genotyping	95%	18%
Median turnaround time	9 days	15 days

recommended genomic biomarkers; it also set out to evaluate potential advantages of cfDNA testing.¹¹ Tissue genotyping included NGS, polymerase chain reaction (PCR) hotspot testing, fluorescent in situ hybridization (FISH) and/or immunohistochemistry (IHC), or Sanger sequencing, and the biomarkers included *EGFR* mutations, *ALK* fusions, *ROS1* fusions, *BRAF* V600E mutation, *RET* fusions, *MET* amplification and *MET* exon 14 skipping variants, *HER2* mutations, and *KRAS* mutations.

The results showed that testing of plasma with a 73-gene NGS at baseline was not inferior to standard-of-care tissue genotyping ($p < 0.0001$ for non-inferiority; Table 1). For the four biomarkers with FDA-approved therapies, the concordance of liquid biopsy to tissue biopsy was greater than 98.2%, with 100% positive-predictive value. The use of cfDNA increased the number of patients with an identified guideline-recommended biomarker by 48%, from 60 patients to 89, including those who had negative results on tissue genotyping (seven patients), those who did not have tissue genotyping (16 patients), and those for whom the amount of tissue was insufficient for testing (six patients). Liquid biopsy allowed guideline-complete genotyping in significantly more patients than tissue biopsy ($p < 0.0001$) and was associated with a significantly shorter median turnaround time ($p < 0.0001$; Table 1).

These results may lead to a change in the current diagnostic paradigm in advanced NSCLC, in which tissue geno-

typing is performed first and liquid biopsy is obtained only when tissue is not available for genomic testing, to one in which liquid biopsy moves upfront (a so-called blood-first approach) and tissue is reserved for IHC testing for PD-L1 and genotyping testing when the results of liquid biopsy testing are negative or inconclusive.

Novel Approach to Plasma Genotyping

One of the potential challenges in plasma genotyping is the identification of tumor-derived mutations of hematopoietic origin (due to a phenomenon called clonal hematopoiesis), generating false-positive results. This poses a major challenge when liquid biopsy is used to evaluate minimal residual disease and for early cancer detection,¹² and it is a potential cause of discordance between tumor and plasma genotyping.¹³

Researchers for the Actionable Genome Consortium sought to investigate the role of an ultra-deep plasma NGS assay with clonal hematopoiesis filtering to guide the treatment of patients with NSCLC.¹⁴ The researchers used a novel approach that incorporated white blood cell sequencing to filter somatic mutations attributable to clonal hematopoiesis. With this approach ultra-deep NGS achieved overall high concordance with tissue testing across a variety of actionable oncogenes, with 75% sensitivity for de novo plasma detection of known oncogenic drivers in 68 of 91 cases and 100% specificity of plasma NGS for patients who had negative

results for oncogenic drivers on tissue testing with NGS in 19 of 19 cases. Furthermore, plasma NGS allowed the identification of four oncogenic drivers among 17 patients in whom the status of oncogenic drivers was unknown because of insufficient tissue. The findings of orthogonal validation with plasma droplet digital PCR (ddPCR) for *EGFR* or *KRAS* mutations were nearly identical to those of plasma NGS in 21 of 22 patients, with only one driver mutation not detected by the NGS assay (this mutation had a low variant allele fraction of 0.04% by ddPCR).

Monitoring Response

The results of the IMMUNO-PREDICT trial were presented at the 2019 ASCO/Society of Immunotherapy for Cancer Clinical Immuno-Oncology Symposium.¹⁵ Using plasma NGS with tagged amplicon sequencing of hotspots and coding regions from 36 genes (Inivata; Granta Park, Cambridge, UK), Guibert et al. analyzed samples (collected at baseline and after 1 month of therapy) from 39 patients who had a response and 47 patients who did not have a response to second-line nivolumab. “Response” was defined as progression-free survival of longer than 6 months, and “no response” was defined as progressive disease at first evaluation. The presence of specific genetic alterations was evaluated according to outcomes. The presence of a targetable oncogenic driver (*EGFR* mutation or *ALK* fusion) was associated with primary resistance to immune checkpoint blockade, and the identification of a *PTEN* and/or *STK11* mutation (b-PS(+)) correlated with a poorer outcome (median progression-free survival, 1.5 vs. 8 months, $p = 0.0007$) compared with b-PS(-). In contrast, *KRAS* and/or *TP53* mutations (b-KP-Tv(+)) predicted improved outcome compared with

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answers,” Dr. Camidge said. “They want to know the latest research and the latest trials.”

“[The doctor] and I discussed my prior and current treatments and before the conversation was over, not only did I have some choices regarding treatment options, but felt extremely hopeful and confident in moving forward with my treatment plan.”

—Patient, United States

However, Dr. Hales recommended some caution be advised to patients seeking any second opinion, remote or otherwise.

“Patients can be beguiled into thinking that the recommendation is the outcome, and if there is one thing true of lung cancer, it’s that it is a dynamic process where recommendations are adjusted and adapted to new findings,”

Dr. Hales said. “I worry that a patient may think she is getting comprehensive guidance from a tertiary center based on initial recommendations. Lung cancer is not a 787 on autopilot.”

Although he values the role of RSOs,

Dr. Hales emphasized that at times, nothing can replace the face-to-face interaction between a physician and the patient, and that physical examinations are a critical part of medical decision making, especially in complex diseases like cancer.

“The future will require these sorts of services to be increasingly available,” Dr. Hales said. “But for now, there are still some practical pieces that must continue to be worked out until we can accept [RSOs] as a widespread standard practice for our patients.” ♦

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MEETING PREVIEW

IASLC 2019 World Conference on Lung Cancer: Collaborative Formats, Novel Data

The world's largest international gathering of clinicians, researchers, and scientists in the field of lung cancer and thoracic oncology—the IASLC 2019 World Conference on Lung Cancer (WCLC)—will kick off on September 7, in Barcelona, Spain.

As in previous years, more than 7,000 delegates representing more than 100 countries are expected to attend the 4-day conference. The variety of attendees illustrates the conference's status as the premier platform for the presentation of new science and the unique networking opportunities it provides.

“The meeting is a great opportunity to interact with national and international colleagues in person, learn what they are involved in, and get updated on progress across specialties,” said IASLC 2019 WCLC Co-Chair Ramon Rami-Porta, MD, PhD, clinical chief of the department of thoracic surgery at Hospital Universitari Mútua Terrassa in Barcelona.



Dr. Ramon Rami-Porta

Cutting-Edge Science

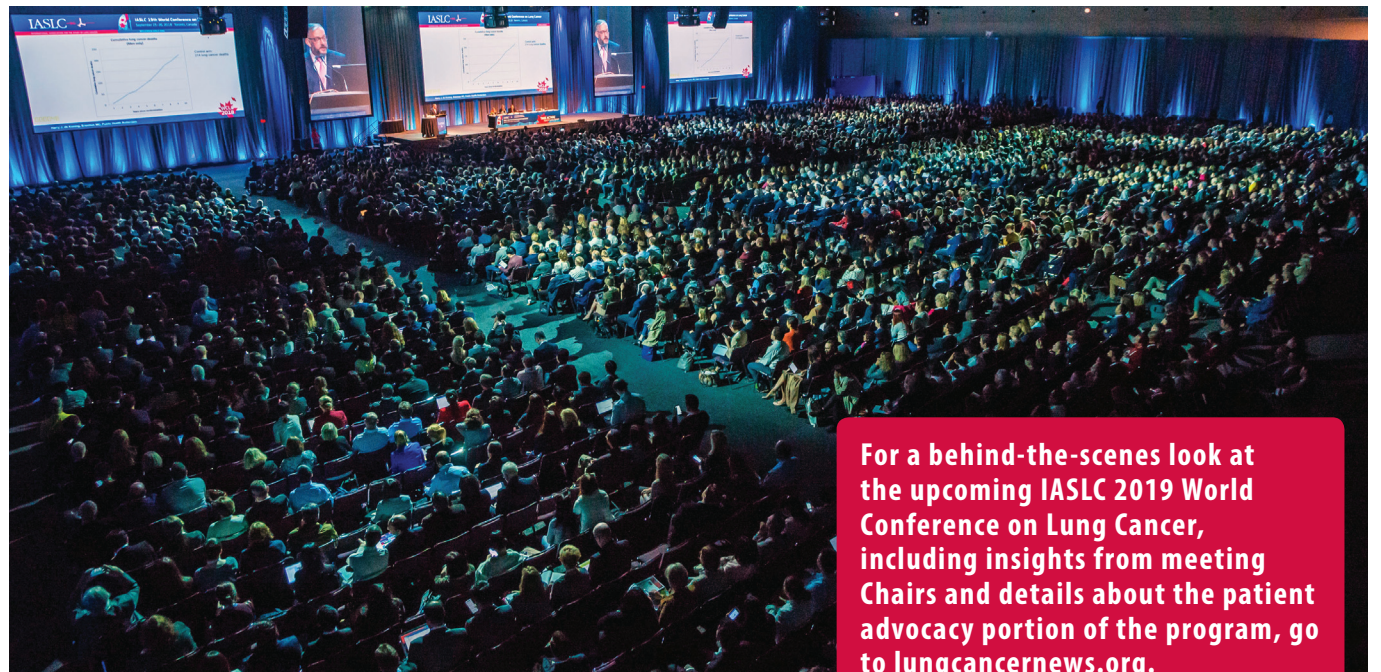
In addition to the networking opportunities, Dr. Rami-Porta looks forward each year to “being an eyewitness to the latest innovations in the field of thoracic oncology that lead to changes in clinical practice,” he said.

Attendees can hear about some of this ground-breaking science during the Presidential Symposium Monday, September 9 at 8:15. This exciting session will include the presentation of the conference's top four rated abstracts.

“Data resulting in a change in clinical practice does not occur every year, but it happened last year in Toronto, and there are good reasons to think that it may happen again this year in Barcelona,” Dr. Rami-Porta said.

In addition to the Presidential Symposium, the conference will include three Plenary Sessions.

“We hope their titles are attractive enough to catch the attention of our attendees,” Dr. Rami-Porta said. “The topics of each session have been selected to attract a multidisciplinary audience,



For a behind-the-scenes look at the upcoming IASLC 2019 World Conference on Lung Cancer, including insights from meeting Chairs and details about the patient advocacy portion of the program, go to lungcancernews.org.

and we are sure attendees will not be disappointed.”

The first Plenary Session, “New Questions with Imaginative Answers,” will take place the morning of Sunday, September 8 at 8:15. This session will include presentations on tumor agnostic—biologically driven treatments, immunotherapy, and artificial intelligence/big data in the treatment of lung cancer.

The next two Plenary Sessions will take place on Tuesday, September 10. The first, “Relevant Aspects of Lung Cancer Management,” is at 9:15 and will include presentations on nurse-led follow-up care, emerging neoadjuvant strategies, lung cancer disparities, and tuberculosis. The second Plenary Session, “Food for Thought in the Management of Thoracic Malignancies,” will take place at 16:15 and will cover topics including survivorship and pleural mesothelioma.

Changes to the Program

This year's Scientific Program also features two small innovations, according to Dr. Rami-Porta.



The 2019 IASLC World Conference for Lung Cancer will provide an opportunity to meet top academic multidisciplinary experts in the thoracic malignancy field and to network with interested colleagues regarding translation of new discoveries into better prevention, diagnosis, staging, and treatment of thoracic malignancies. The meeting will be an excellent place to create new contacts, share new ideas for projects, and promote collaboration in thoracic malignancy research.

—Dr. Enriqueta Felip

The early-morning sessions are now called Interactive Breakfast Sessions. The sessions will maintain the same format

used in previous WCLCs—presentation of a topic followed by discussion with the audience—but this year, some of these sessions will have an increased number of speakers to widen the points of view and keep good balance regarding geography and specialty.

In addition, the duration of the invited lectures in some of this year's sessions have been shortened to allow more presentations, thereby covering topics in a more comprehensive way, Dr. Rami-Porta said.

“This will make the sessions more dynamic and will facilitate the exchange of opinions both among presenters and among the audience,” he said.

Encouraged to Attend

Outside of the plenary sessions, attendees will once again have multiple opportunities for networking. The meeting will begin on Saturday, September 1 at 19:00 with the Opening Ceremony & Keynote Presentation, which will include the IASLC Distinguished Awards Presentation. Immediately after attendees are invited to the Welcome Reception at 20:30.

Coffee breaks are scheduled throughout the day and are also excellent opportunities to catch up with colleagues.

“Nothing can replace face-to-face meetings,” Dr. Rami-Porta said. “I believe in the benefits of personal interaction. I have often thought that

what may seemingly be a very casual conversation over coffee can save a life, perhaps, many years later.” ♦

From its first appearance on Twitter in 2013, #LCSM (Lung Cancer Social Media) has grown from a few tweets a week into the most-used cancer hashtag during the 2019 ASCO Annual Meeting. Search for tweets containing the hashtag #LCSM to view the #LCSM feed.



The #LCSM community seeks to educate, develop public support, end the stigma, and facilitate successful treatments for the leading cause of cancer death worldwide: lung cancer. The community includes all of those affected by lung cancer, including: patients, caregivers, family members, health-care providers, researchers, clinicians, advocates, funders, government organizations, and industry.

Once each month, the community comes together on Twitter for #LCSM Chat. The #LCSM Chat website (lcschat.com) is home to a list of upcoming chat topics as well as transcripts of past chats. Search for tweets containing the hashtag “#LCSM” to view the #LCSM feed. #LCSM Chat topics for the remainder of 2019 are listed below. All chats start on a Thursday evening at 8:00 pm ET and last 1 hour.

- **Sep 19** World Lung (#WCLC19) Wrap-Up
- **Oct 3** The Path to Research Advocacy
- **Nov 07** Lung Cancer Awareness—Are We Making a Difference?
- **Dec 05** Ho Ho How to Do Holidays with Cancer

A DEEPER DIVE



Improving Lung Nodule Evaluation Through Identification of Additional Features

By David Yankelevitz, MD

The article “Novel high-resolution computed tomography-based radiomic classifier for screen-identified pulmonary nodules in the National Lung Screening Trial”¹ outlines the tremendous need for developing techniques to distinguish benign from malignant nodules, especially small lesions. This is especially important with the endorsement for lung cancer screening now in place in multiple countries based in part on the positive NELSON trial; these results will surely lead to further uptake of screening.² In addition, with the inclusion of the large number of incidental nodules found outside of the screening context, the authors describe a “potential emerging global epidemic of newly detected lung nodules.” With continued improvements in scanner technology and availability, as well as computer-assisted means for detecting small nodules, this challenge will surely continue to be in the forefront.

Tackling False Positives

One of the widely accepted challenges in screening (and also for the incidental nodule) has been what is described as the high rate of false-positive results. Nodules may require additional work-up, possibly leading to invasive procedures and their potential for harm; in some cases, these nodules turn out to be benign, in which case patients go through potentially unnecessary thoracic biopsies or explorations. Various nodule-management protocols have been developed for the purpose of minimizing these false positives, primarily using a combination of size thresholds for initiating work-up and then using growth estimates based on follow-up scanning. There is clearly a need to continue to make these evaluations more efficient.

The method outlined in the paper

relies on the use of radiomics, a method of extracting features from images and determining their predictive value. For their analysis, the authors chose a dataset of nodules from the publicly available database of the National Lung Screening Trial, which was the first and largest of the trials to demonstrate a mortality reduction for lung cancer screening. The availability of this type of large, well-documented database is an important resource, as it will continue to facilitate these types of analyses well into the future.

The approach taken for their evaluation involved the analysis of 57 different features. These particular features were chosen specifically with a view toward incorporating ones already considered to have clinical significance. Using a variety of well-known statistical techniques, the authors were able to optimize their prediction model using only eight features, demonstrating an area under the curve of (AUC) of 0.94. This represents a highly promising result, although the authors suggest that additional validation using other datasets will be necessary.

Diagnostic Factors

However, when looking more closely at these results, a challenging aspect appears in that nearly all of the diagnostic information can be explained by nodule size alone. The AUC just using volume or other measures that reflect size was at least 0.9. Although the authors attempted to account for this by eliminating size-dependent measures and still show a high AUC, it seems likely that at least some of the remaining metrics remain size dependent.

Because size measurements provide so much of the diagnostic information, it is difficult to imagine that once size is accounted for when making a diagnostic consideration about a particular nodule



Dr. David Yankelevitz

that the additional small bit of information provided by other features would substantially change management. This point has been emphasized previously by Reeves et al.³ Several other considerations also dampen the enthusiasm for this approach. The first is the use of simple dichotomization when comparing benign versus malignant, as this does not account for the extensive variation within each of these categories. It seems likely that the different types of benign nodules (infectious, chronic infectious, and benign tumors) would have very different features; similarly, different types of malignant tumors with known differences in growth patterns would also prove quite different. Beyond that, the database analyzed was not representative of the distribution of nodule types in the screening population, with nearly 50% of the nodules chosen proving malignant—a point that the authors recognize. Additionally, the scan parameters in the National Lung Screening Trial database are already outdated, with slice thickness of 2.5 mm compared to modern protocols, which routinely obtain submillimeter slice thickness. Finally, one of the most important clinical pieces of informa-

IN REFERENCE TO:

Peikert T, Rajagopalan S, Karwoski RA, et al. Novel high-resolution computed tomography-based radiomic classifier for screen-identified pulmonary nodules in the National Lung Screening Trial. *PLoS One*. 2018;13(10). e0196910

tion that greatly affects decision making about the type of nodule is whether it is identified in a baseline round or subsequent round of imaging; this was not explicitly accounted for in the analysis. Here the effect of size is in the opposite direction; for a baseline nodule, the larger the size the more likely it proves malignant, whereas for new nodules, the relationship is more complex, but after a certain threshold, increasing size implies a decreased likelihood of malignancy.

In conclusion, the overarching goal of this approach to identify additional features of “screened” nodules so as to better classify them is of great importance, and it seems likely that additional information can be captured using various radiomic features. However, it also seems likely that a more nuanced approach that includes higher-quality images, a much larger database of cases with consideration for various types of nodules, improved feature selection, and further inclusion of additional clinical information will be needed before we can realistically change current approaches to nodule management. Nevertheless, all of these considerations can be addressed. This paper demonstrates the great potential for this strategy, which should continue to improve over time. ♦

About the Author: Dr. Yankelevitz is a professor of radiology and the director of the Lung Biopsy Service at the Icahn School of Medicine at Mount Sinai. Dr. Yankelevitz is a named inventor on a number of patents and patent applications related to the evaluation of diseases of the chest including measurement of nodules. Dr. Yankelevitz has received financial compensation for licensing of these patents. In addition, he is a consultant and co-owner of Accumetra, a private company developing tools to improve the quality of CT imaging and is on the medical advisory board for Grail a company that does blood tests for early detection of cancer.

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NOW ENROLLING:

Patients with advanced/metastatic NSCLC harboring *MET* alterations

VISION: A Phase 2, Single-Arm Clinical Trial With Tepotinib¹

Tepotinib is under clinical investigation and has not been proven to be safe and effective. There is no guarantee tepotinib will be approved in the sought-after indication by any health authority worldwide.

Description

Phase 2, single-arm, multi-cohort trial investigating the safety and efficacy of tepotinib, an investigational oral and once-daily MET inhibitor, in patients with advanced/metastatic NSCLC harboring *MET*ex14 skipping or *MET* amplification.

Study design

- Stage IIIB/IV NSCLC
 - All histologies
 - Tissue- or blood-based *MET* alterations
 - 0–2 prior lines of therapy
 - Regions: EU, US, Asia
- N ≤ 120 patients

Cohort A
*MET*ex14 skipping

Cohort B
MET amplification

Tepotinib
500 mg orally
once daily*

Select endpoints

- Primary endpoint**
- ORR by independent review
- Secondary endpoints**
- ORR by investigator assessment
 - DOR
 - Objective disease control
 - PFS
 - OS
 - Safety
 - Health-related QoL
 - Pharmacokinetics

Analyses sets include detection of *MET*ex14 skipping by:

- Liquid biopsy
- Tissue biopsy

Key inclusion criteria

- Patients ≥ 18 years of age with histologically confirmed advanced (stage IIIB/IV) NSCLC (all histologies)
- *MET*ex14 skipping or *MET* amplification (plasma and/or tumor biopsy sample)
- Treatment-naïve or pre-treated with no more than 2 lines of prior therapy
- Prior therapy with a checkpoint inhibitor is permitted

Key exclusion criteria

- *EGFR* activating mutations or *ALK* rearrangements that predict response to anti-*EGFR* or anti-*ALK* therapy
- Active brain metastases, or brain metastases as the only measurable lesion
- Prior treatment with other agents targeting the *MET* pathway

1. ClinicalTrials.gov. Available at clinicaltrials.gov/show/NCT02864992, date last accessed 22 July 2019.
*Treatment continues until progression of disease, withdrawal of consent, or development of unacceptable toxicities.
ALK, anaplastic lymphoma kinase; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor; EU, European Union; *MET*, mesenchymal-epithelial transition factor; *MET*ex14, *MET*exon14; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; RECIST, Response Evaluation Criteria in Solid Tumors; US, United States.



This information is current as of July 2019.
July 2019 GBPMLR/MULOP/0519/0009

To learn more about VISION,
please visit ClinicalTrials.gov
(NCT02864992)
For more information, contact
Merck KGaA at: +49 6151 72 5200



NOW ENROLLING:

Patients with advanced/metastatic NSCLC with *MET* amplification who have relapsed on prior *EGFR* TKI

INSIGHT 2: A Phase 2, Single-Arm Clinical Trial With Tepotinib + Osimertinib¹

Tepotinib is under clinical investigation and has not been proven to be safe and effective. There is no guarantee tepotinib will be approved in the sought-after indication by any health authority worldwide.

Description

Phase 2, single-arm trial investigating the safety and efficacy of tepotinib, an investigational oral and once-daily MET inhibitor, in combination with osimertinib in patients with *MET*-amplified advanced/metastatic NSCLC harboring activating *EGFR* mutations and acquired resistance to prior 1st, 2nd or 3rd generation *EGFR* TKIs.

Study design

- Locally advanced/metastatic *EGFR*+ NSCLC
 - *MET* amplification
 - Acquired resistance to prior *EGFR* TKI
- N = 90 patients

Tepotinib 500 mg
orally once daily*
+
Osimertinib 80 mg
orally once daily*

Select endpoints

- Primary endpoints**
- ORR by independent review
 - Dose-limiting toxicity (safety run-in only)
- Secondary endpoints**
- Safety
 - ORR by investigator assessment
 - DOR
 - PFS
 - OS
 - Disease control
 - Health-related QoL
 - Pharmacokinetics

Key inclusion criteria

- Histologically confirmed locally advanced or metastatic NSCLC with documented, activating *EGFR* mutation
- *MET* amplification
- Acquired resistance on prior *EGFR* TKI

Key exclusion criteria

- Inadequate hematological, liver, renal, or cardiac function, or hypertension uncontrolled by standard therapies
- Spinal cord compression or brain metastasis unless asymptomatic, stable or not requiring steroids for at least 2 weeks prior to start of study

1. ClinicalTrials.gov. Available at: clinicaltrials.gov/show/NCT03940703, date last accessed 22 July 2019.
*Treatment continues until progression of disease, withdrawal of consent, or development of unacceptable toxicities.
DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor; *MET*, mesenchymal-epithelial transition factor; NSCLC, non-small cell lung cancer; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; QoL, quality of life; TKI, tyrosine kinase inhibitor.



This information is current as of July 2019.
July 2019 GBPMLR/MULOP/0519/0006

To learn more about INSIGHT 2,
please visit ClinicalTrials.gov
(NCT03940703)
For more information, contact
Merck KGaA at: +49 6151 72 5200



MEETING HIGHLIGHTS

Lung Cancer Research Highlights from the 2019 ASCO Annual Meeting

By Kara Nyberg, PhD

The 2019 Annual Meeting of the American Society of Clinical Oncology (ASCO) featured hundreds of lung cancer abstracts encompassing the full spectrum of this malignancy. This article highlights some of the most important NSCLC and SCLC research presented at ASCO that will help shape future areas of inquiry and, ultimately, real-life clinical practice.

Neoadjuvant Therapy in NSCLC

As immune checkpoint inhibitors become part of standard practice in advanced NSCLC, forays into earlier stages of disease offer new promise. Small pilot studies have indicated that immune checkpoint inhibitors might benefit patients with resectable NSCLC when used prior to surgery. “Upregulation of tumor PD-L1 has been shown to be critical for the spread and survival of lung metastasis in murine models of lung adenocarcinoma, supporting the testing of immune checkpoint inhibitors in the neoadjuvant setting to prime the intratumoral immune response and eradicate metastatic disease,” according to Tina Cascone, MD, PhD, of the University of Texas MD Anderson Cancer Center.

Two neoadjuvant studies presented at ASCO, LCMC3 and NEOSTAR, were designed to investigate these initial observations more thoroughly. LCMC3, presented by David J. Kwiatkowski, MD, PhD, of the Dana-Farber Cancer Institute, is an ongoing single-arm phase II trial evaluating two cycles of neoadjuvant atezolizumab in patients with stage IB to IIIB NSCLC (Abstract 8503). NEOSTAR, presented by Dr. Cascone, is a now-completed randomized phase II trial

that assessed three cycles of neoadjuvant nivolumab, either alone or in combination with a single dose of ipilimumab, in patients with stage IA to IIIA NSCLC (Abstract 8504).

Neoadjuvant immunotherapy proved encouraging based on the primary efficacy endpoint of major pathologic response (MPR), defined as 10% or fewer viable tumor cells in the surgical resection specimen. In LCMC3, the MPR rate was 19% among 77 evaluable patients who received neoadjuvant atezolizumab (Fig. 1). In NEOSTAR, the MPR rate was 19% among 21 evaluable patients who received neoadjuvant nivolumab and 44% among 16 evaluable patients who received neoadjuvant nivolumab plus ipilimumab.

Each of these regimens was relatively well tolerated, with grade ≥ 3 treatment-related adverse events (TRAEs) occurring in only 6% to 13% of patients. Most patients were able to proceed to surgery (89% resection rate in both trials) due to low rates of disease progression ($\leq 5\%$).

Maximilian Diehn, MD, PhD, of the Stanford Cancer Institute, who discussed the LCMC3 and NEOSTAR trials, acknowledged the favorable findings and noted that the MPR rates are consistent with those conferred by neoadjuvant multiagent chemotherapy. For example, in a study conducted in 41 patients with stage IB to IIIA NSCLC, four cycles of neoadjuvant cisplatin, docetaxel, and bevacizumab yielded an MPR rate of 27%.¹

However, Dr. Diehn also emphasized that additional research will be needed to bolster the results. First, MPR has not been validated as a surrogate endpoint for OS, meaning that longer follow-up—preferably in the setting of larger randomized studies—will be required to

determine whether neoadjuvant immunotherapy truly makes a difference in prolonging survival.

Second, both LCMC3 and NEOSTAR enrolled all-comers, potentially exposing some patients to unsuitable therapy. “I think we have a major unmet need for developing biomarkers for personalized treatment in this area,” Dr. Diehn remarked. Whereas both PD-L1 expression and tumor mutation burden (TMB) have been shown to independently predict the response to selected immunotherapy regimens in the metastatic setting (Abstract 9016), these biomarkers may not apply in the neoadjuvant setting or to all types of immune checkpoint inhibitors. In both LCMC3 and NEOSTAR, positive PD-L1 expression showed a significant but moderate correlation with MPR; in LCMC3, TMB and genes commonly mutated in NSCLC did not.

Finally, Dr. Diehn suggested that combined treatment with immunotherapy and chemotherapy may be much more effective in the neoadjuvant setting than either therapeutic class alone. Indeed, early results from small studies of carboplatin/paclitaxel combined with either nivolumab or atezolizumab have yielded MPR rates ranging from 64% to 80%.^{2,3} According to Dr. Diehn, this suggests that, “as in the advanced setting, the combination of

immunotherapy and chemotherapy may be most active in [the neoadjuvant] setting,” particularly when patients are not selected based on predictive biomarkers. In fact, four separate phase III studies of neoadjuvant immunotherapy in combination with a platinum doublet are cur-

rently underway to help address this very issue: CheckMate 816 with nivolumab (NCT02998528), KEYNOTE-617 with pembrolizumab (NCT03425643), IMpower030 with atezolizumab (NCT03456063), and AEGEAN with durvalumab (NCT03800134).

Definitive Concurrent Chemoradiation in NSCLC

Improving on definitive platinum-based doublet chemoradiotherapy for patients with unresectable stage III NSCLC remains elusive in light of negative results from NRG-LU001, a randomized phase II trial that failed to show improved outcomes with the addition of metformin to concurrent chemoradiotherapy (Abstract 8502). The rationale for NRG-LU001 was sound: Although metformin is a well-established diabetes medication that influences glucose metabolism, the agent has also been found to activate tumor-suppressing pathways and enhance the response to radiotherapy and chemotherapy in preclinical NSCLC models. Unfortunately, metformin failed to deliver when tested in humans based on the NRG-LU001 data presented by Theodoros Tsakiridis, MD, PhD, of McMaster University.

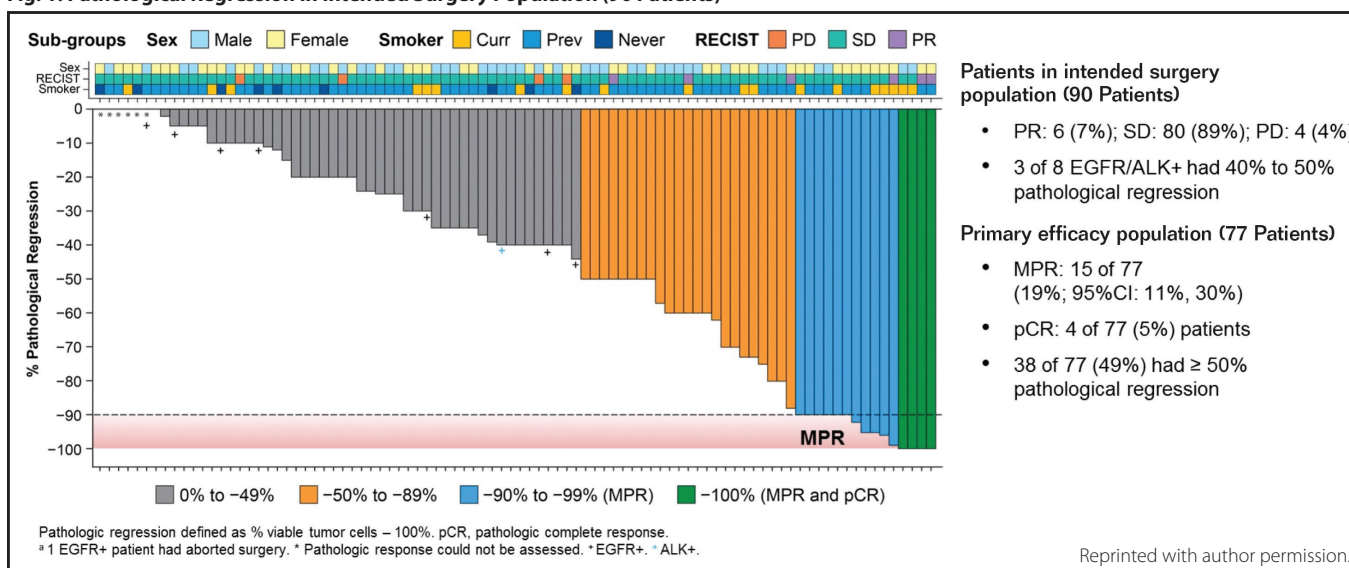
“As in the advanced setting, the combination of immunotherapy and chemotherapy may be most active in [the neoadjuvant] setting,” particularly when patients are not selected based on predictive biomarkers.

—Dr. Maximilian Diehn

NRG-LU001 included 167 patients with inoperable stage IIIA/IIIB NSCLC but without comorbid diabetes. Participants were stratified by performance status, disease histology, and clinical stage and randomly assigned to standard concurrent chemoradiotherapy (carboplatin/paclitaxel + full-dose radiotherapy) either alone or combined with concurrent metformin. In both arms, concurrent chemoradiotherapy was administered for 6 weeks, followed by 6 weeks of consolidation chemotherapy (plus metformin in the investigational arm).

NRG-LU001 did not meet the primary endpoint of improved PFS with the addition of metformin to chemoradiotherapy. Median PFS in the intention-to-treat population reached 12.2 months in the group that received metformin compared with 16.6 months for the group that did not (HR: 1.15; 95% CI: 0.77-1.73; $p = 0.2441$). The addition of metformin to chemoradiotherapy also did not improve median OS (40.1 vs 38.5 months; HR:

Fig. 1. Pathological Regression in Intended Surgery Population (90 Patients)



'Blood-First' Approach from page 4

b-KP-Tv(-) (median progression-free survival, 11 vs. 2 months, $p = 0.0088$).

Combining these results, the authors were able to develop an immune score: a low immune score was characterized by an oncogenic driver and/or b-PS(+) and/or b-KP-Tv(-), and a high immune score, by no driver, b-PS(-), and b-KP-Tv(+). The progression-free survival was significantly shorter for patients with a low immune score than for patients with a high immune score (Table 2). Furthermore, molecular response was correlated with a longer median progression-free survival (14 months for patients with an early decrease in circulating tumor DNA compared with 2 months for patients with increased levels of circulating tumor DNA; $p < 0.0001$; HR: 2.7); when a cut-off of 30% and 50% of plasma response was used, the ability of circulating tumor DNA to predict radiographic response increased (HR of 4.0 and 4.17, respectively).

These data further confirm the predictive role of *STK11*, *KRAS*, and *TP53* mutations detectable in plasma on the activity of immune checkpoint inhibitors in NSCLC^{16,17} and support the potential use of NGS genotyping on circulating tumor DNA in the pretreatment evaluation of patients who are candidates for immunotherapy.

Patient Perspective

The advent of targeted therapy and immunotherapy in advanced NSCLC has led to a growing population of people living longer with the disease, which alters the implications of research and post-treatment surveillance. For example, issues such as long-term effects, which were once unimportant because of the short survival expectations, now must be evaluated. The patient perspective is essential to the discussion of genomic testing with liquid biopsy. Patient-reported outcomes after tissue and liquid biopsy testing should be com-

Table 2. Correlation of Immune Score with Outcome in IMMUNO-PREDICT Trial

Immune Score ^a	Progression-Free Survival	P Value
Low	2 months	0.0001; HR = 2.7
High	14 months	

^aLow immune score: an oncogenic driver and/or b-PS(+) and/or b-KP-Tv(-); high immune score: no driver, b-PS(-), and b-KP-Tv(+).

pared. Cost is another important factor, as the high cost can be prohibitive; not all NGS testing is covered by Medicare or third-party insurers (lab-developed testing systems are typically not covered). Also, messaging about biomarkers must be consistent to avoid confusion about why biomarker testing is important, who should have testing, and when testing should be done.

The advent of targeted therapy and immunotherapy in advanced NSCLC has led to a growing population of people living longer with the disease, which alters the implications of research and post-treatment surveillance.

In its 2018 Post-Treatment Surveillance Workshop, the National Cancer Institute addressed the importance of patient perspectives, and Janet Freeman-Daily, a lung cancer advocate, spoke about the importance of the patient voice. She said that surveillance must be meaningful to patients, not just research, and she encouraged attendees to learn what matters most to their patients and to engage in true shared decision-making. ♦

About the Authors: Dr. Rolfo is the director of the Thoracic Medical Oncology and the Early Clinical Trials at the University of Maryland Marlene and Stewart Greenebaum Comprehensive Cancer Center. Ms. Alexander is a certified medical writer and the education director at the American Medical Writers Association.

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To embrace the study of the etiology, epidemiology, prevention, diagnosis, treatment, and all other aspects of lung cancer and other thoracic malignancies; to provide education and information about lung cancer and other thoracic malignancies to IASLC members, to the medical community at large, and to the public; to use all available means to eliminate lung cancer and other thoracic malignancies as a health threat for the individual patient and throughout the world.

Names and News

Christian Rolfo, MD, PhD, MBA, Dr.h.c., was recently appointed vice president of The International Society of Liquid Biopsy (ISLB). This nonprofit organization, founded in 2017, aims to erase restrictions of liquid biopsy implementation in routine clinical practice, either in individual countries or across specialties. The society will hold its annual congress April 3-4, 2020, in Barcelona. ♦



GLOBAL INITIATIVES

Ireland's Complex Healthcare System and Its Relation to Innovative Ways for Patients to Access Trials

By Linda Coate, MD, FRCPI, and Hazel O'Sullivan, MB, Bch, BAO, MRCPI

The Republic of Ireland has a publicly funded healthcare system, financed by general taxation.¹ Approximately 43% of the population also has private health insurance.² Approximately 35% of patients have a “medical card,”³ which entitles them to free hospital attendances, general practitioner visits, and heavily discounted medications. Many citizens have both means to access healthcare. All Irish citizens aged 70 and older are entitled to a modified medical card but may have to pay for medication, and patients younger than age 70 are means tested following their medical card requests. All citizens are allowed to apply for a drug subsidy scheme, which caps payments to community pharmacies (including a number of high-cost oncology drugs taken orally and dispensed monthly). Drug costs for patients undergoing cancer treatment in a private hospital are borne

by the patients' insurance company. Drug acquisition costs, but not cost of care, are borne by the government system for patients with insurance being treated in a public hospital. This complex, overlapping, and often confusing landscape of public and private medicine in Ireland makes an already intricate and often emotive pharmacoeconomic area in medicine difficult to examine and measure, even within—or perhaps particularly within—the presumed healthcare homogeneity of the European Union (EU).

Relation Between Regulatory Approval, Treatment Cost

Ireland is a member of the EU, and, therefore, medicines in Ireland are subject to regulatory approval as a member state. The European Medicines Agency (EMA) is responsible for the scientific evaluation, supervision, and safety monitoring of all medicines in Europe.⁴ Cancer medicines must be approved by the EMA prior to pharmaceutical companies' application

for market authorization in Ireland. Following the application, the National Centre for Pharmacoeconomics (NCPE) is the government agency responsible for decisions regarding the reimbursement of new cancer drugs. The NCPE considers the therapeutic benefit of the agent, its cost-effectiveness, and budgetary effects. The NCPE will carry out a “rapid review” of the application within 4 weeks (in practice, this can take much longer). If it is felt a full economic evaluation is required, a health technology assessment will be performed within 90 days (delays at this point are also possible). Once a positive recommendation has been made by the NCPE, the result is returned, and a national chemotherapy protocol is written. An Irish physician can prescribe a medicine not subsidized publicly once it has had EMA approval, but insurance companies usually fund the cost of the agent following the recommendations of the public system. Increasingly, demands for off-label use of cancer drugs

have resulted in patients paying out of pocket for their cancer medications. This is also true for those medications that are licensed, but not yet reimbursed (the so-called “valley of death” in a memorable plenary session at the European Society for Medical Oncology 2016 Congress).

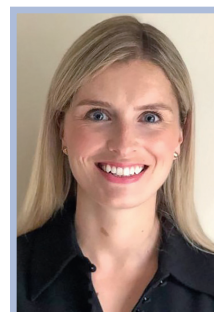
Figure 1 outlines the dates of the recent NSCLC treatments

approved by the EMA. This generally temporally follows, but is broadly in line with U.S. Food and Drug Administration approvals. Figure 2 lists the treatments funded in Ireland along with reimbursement dates. Note that prior to April 2018, patients with lung cancer in Ireland did not have access to immune checkpoint inhibitors for any indication. Until the time of writing of this article, funding for immunotherapy was confined to those patients with PD-L1 expression of greater than 50%. Nivolumab is now available for treatment of patients in the second line; atezolizumab and durvalumab await reimbursement decisions.

Currently, patients with a *T790M* *EGFR* mutation cannot receive osimertinib unless they pay out of pocket for the drug achieved sometimes by crowdfunding. Astra Zeneca first applied to the NCPE for reimbursement in February 2016, but the company's request was denied following a pharmacoeconomic assessment. Further applications have been made but have been rejected, as it was deemed not cost effective. However, the drug is under reassessment.⁵ For patients with *ALK*-positive disease, there is publicly reimbursed access to crizotinib in the first-line setting and to both ceritinib and alectinib in the second-line setting. The disparity and inconsistency between regulatory approval and the decision to fund cancer medicines in Ireland has left a “vulnerability gap.” This gap means that the value of medicine at price-point purchase (sometimes because of hastily negotiated reimburse-



Dr. Linda Coate



Dr. Hazel O'Sullivan

Fig. 1. EMA-Approved NSCLC Treatments

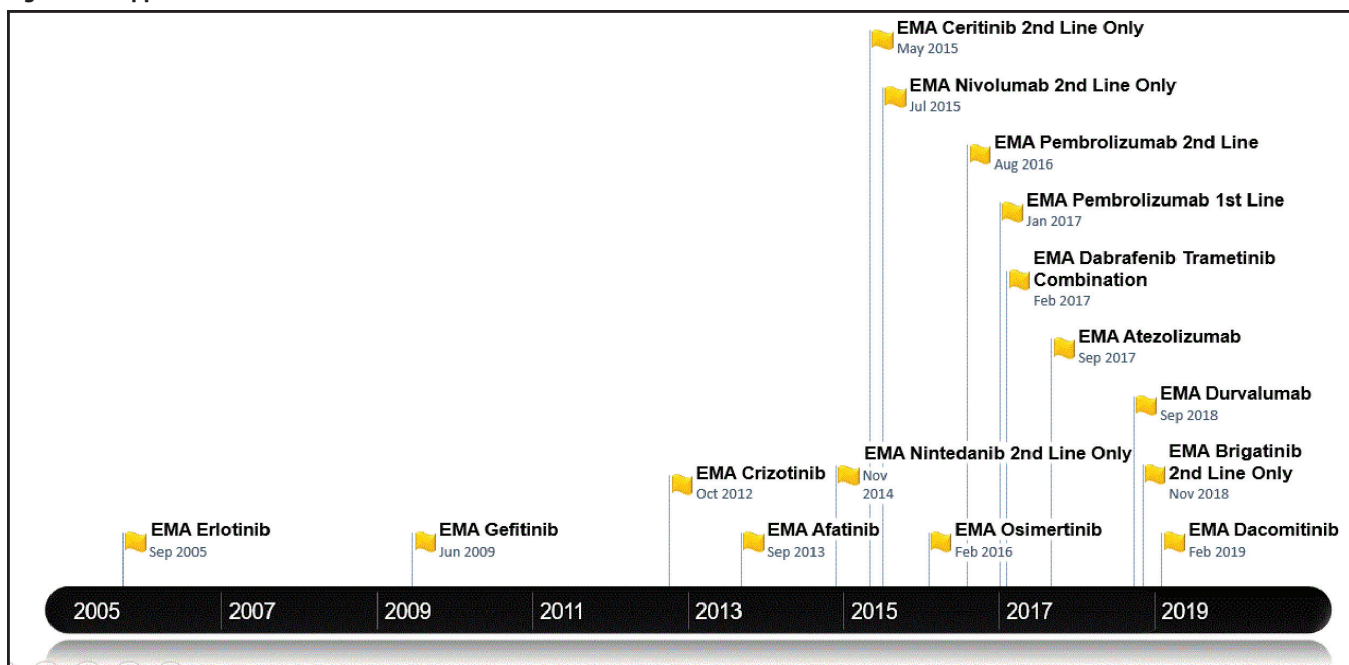
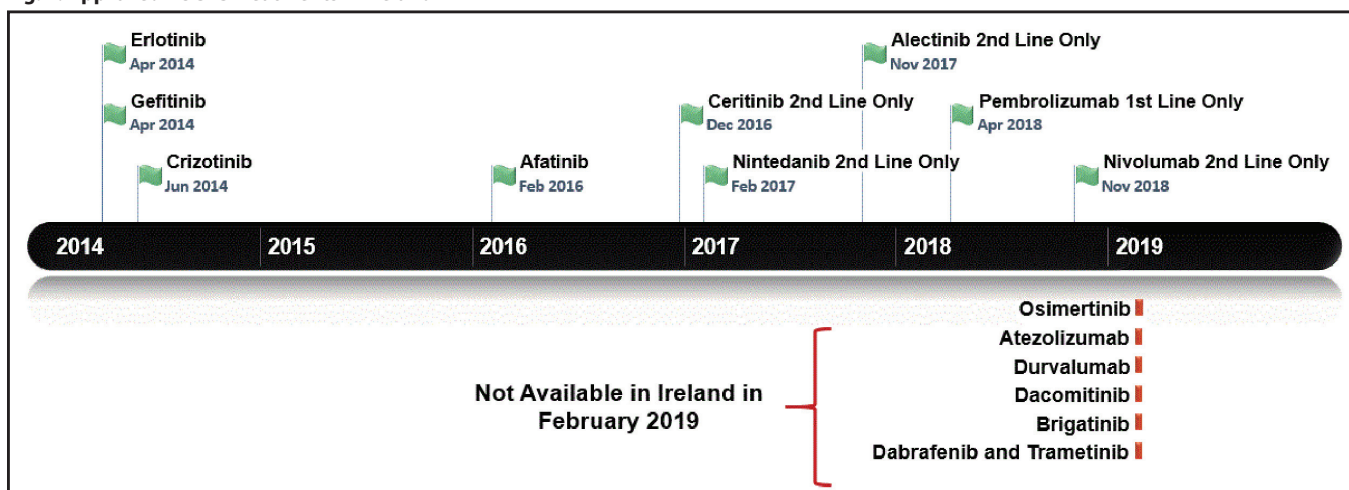


Fig. 2. Approved NSCLC Treatments in Ireland



Investigating the potential concomitant inhibition of TGF- β and PD-L1 with bintrafusp alfa (proposed INN for M7824) in multiple tumor types.

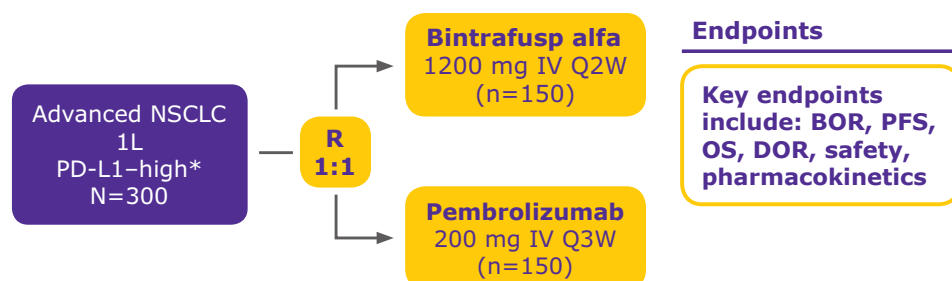
Bintrafusp alfa is under clinical investigation and has not been proven to be safe and effective. There is no guarantee that bintrafusp alfa will be approved in the sought-after indication by any health authority worldwide.

INTR@PID LUNG 0037¹ Now Enrolling



INTR@PID LUNG 0037 (NCT03631706) is a phase 2, randomized, multicenter, open-label study comparing bintrafusp alfa vs pembrolizumab in the first-line treatment of patients with advanced NSCLC with high PD-L1* expression levels.

Study Design | Global



Key eligibility criteria[†]

- Participants must have histologically confirmed advanced NSCLC with PD-L1-high* tumor expression

Key exclusion criteria[†]

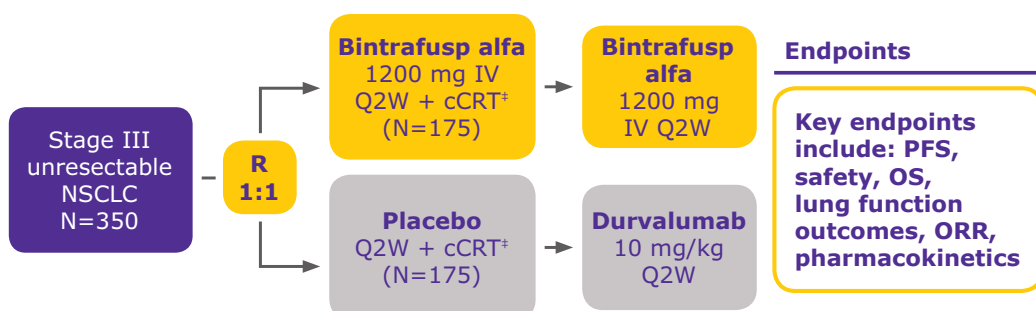
- Participants must not have received prior systemic therapy for advanced NSCLC and must not have *EGFR*-sensitizing (activating) mutations, *ALK* translocation, *ROS1* rearrangement, or *BRAF* V600E mutation

INTR@PID LUNG 0005² Now Enrolling



INTR@PID LUNG 0005 (NCT03840902) is a phase 2, multicenter, double blind, randomized, controlled study evaluating bintrafusp alfa with concurrent chemoradiation followed by bintrafusp alfa versus concurrent chemoradiation plus placebo followed by durvalumab in patients with unresectable stage III NSCLC.

Study Design | North and South America, Europe, Australia, and Asia



Key eligibility criteria[†]

- Participants must have histologically confirmed stage III locally advanced, unresectable NSCLC, ECOG PS of 0 or 1 and adequate pulmonary function

Key exclusion criteria[†]

- Participants must not have mixed small cell and NSCLC histology or received prior systemic therapy for NSCLC

* PD-L1-high status as determined by central PD-L1 test or by prior testing using PD-L1 IHC 22C3 pharmDx assay.

[†] For a full list of all inclusion and exclusion criteria, please visit www.clinicaltrials.gov.

* cCRT consists of 60 Gy of radiation therapy in combination with standard chemotherapy (cisplatin/etoposide, cisplatin/pemetrexed or carboplatin/paclitaxel).

1L, first line; ALK, ALK receptor tyrosine kinase; BOR, best overall response; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; IHC, immunohistochemistry; IV, intravenous; NSCLC, non-small cell lung cancer; OS, overall survival; PD-L1, programmed cell death 1 ligand 1; PFS, progression-free survival; Q2W, every 2 weeks; Q3W, every 3 weeks; R, randomized; TGF- β , transforming growth factor- β .

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1.03; 95% CI: 0.64-1.68; $p = 0.8910$), the median time to locoregional failure (HR: 0.91; 95% CI: 0.51-1.62), or the median time to distant failure (HR: 1.29; 95% CI: 0.71-2.34).

“It should be noted that in this study, we observed higher-than-expected survival outcomes compared to recently reported phase III trials,” Dr. Tsakiridis remarked.

First-Line Treatment of Metastatic NSCLC

In metastatic NSCLC, two randomized phase III trials—RELAY and a study conducted at the Tata Memorial Hospital in India—assessed whether augmenting targeted therapy with antiangiogenic therapy or cytotoxic chemotherapy, respectively, could improve outcomes in the first-line setting for patients with *EGFR*-mutated disease.

Although dual blockade of the *EGFR* and *VEGF* pathways might lead to synergistic antitumor activity, Japanese trials that have evaluated this approach using a first-generation *EGFR* tyrosine kinase inhibitor (TKI) in combination with bevacizumab (ie, JO25567, NEJ026) have yielded mixed results.^{4,5} The RELAY trial (Abstract 9000) differed from these prior studies in that (a) it was a global study conducted at multiple sites in Asia, Europe, and North America and (b) it featured ramucirumab, which targets *VEGF* receptor 2, instead of bevacizumab, which targets *VEGF* ligands.

RELAY included 449 patients with stage IV NSCLC harboring common, actionable *EGFR* mutations (exon 19 deletion or exon 21 L858R); they were randomly assigned to receive erlotinib

plus ramucirumab (ER) or erlotinib plus placebo (EP). The trial met the primary endpoint by demonstrating a significant 7-month improvement in median PFS with the addition of ramucirumab to erlotinib, compared to placebo (19.4 vs 12.4 months; HR: 0.591, 95% CI: 0.461-0.760; $p < 0.0001$). The improvement in PFS appeared to be driven by a prolonged duration of response for ER and EP, respectively (18.0 vs 11.1 months) rather than an improvement in response rate (76% vs 75%). Moreover, the PFS benefit conferred by ramucirumab may also extend to OS (HR: 0.832, 95% CI: 0.532-1.303), although the data are not yet fully mature.

In terms of toxicity, ramucirumab led to a higher rate of grade ≥ 3 TRAEs when added to erlotinib compared with placebo (72% vs 54%); however, discontinuation rates due to TRAEs were similar for the respective arms (13% vs 11%). The principal toxicity associated with ramucirumab was hypertension (all grades: 45% vs 12% with placebo; grade 3: 24% vs 5% with placebo).

The phase III trial conducted at the Tata Memorial Hospital assessed whether adding pemetrexed/carboplatin to gefitinib improved median PFS in 350 patients with *EGFR*-mutated, unresectable stage IIIB or stage IV NSCLC (Abstract 9001). Eligibility for this trial was less stringent and included patients with an Eastern Cooperative Oncology Group performance status of 0 to 2; activating *EGFR* mutations in exon 19, 21, or 18; and it permitted individuals with brain metastases.

Like RELAY, the Tata Memorial trial successfully documented a significant improvement in PFS, the primary endpoint, with gefitinib plus chemotherapy versus gefitinib alone (16.0 vs 8.0

months; HR: 0.51, 95% CI: 0.39-0.66; $p < 0.0001$). However, unlike RELAY, this improvement was driven by a higher response rate (75% vs 63%; $p = 0.01$) and depth of response (median tumor size reduction: 56.4% vs 43.5%; $p = 0.002$). The study also demonstrated a significant improvement in median OS with the addition of pemetrexed/carboplatin to gefitinib versus gefitinib alone (not reached vs 17.0 months; HR: 0.45, 95% CI: 0.31-0.65; $p < 0.0001$).

As expected, adding chemotherapy to gefitinib increased toxicity in comparison to gefitinib alone. Clinically relevant grade ≥ 3 adverse events occurred in 51% in the investigational arm versus 25% in the control arm, largely driven by increases in hematologic events. Additionally, 17% of patients in the investigational arm discontinued pemetrexed due to toxicity, whereas the rate of gefitinib discontinuation in either arm was $\leq 1\%$.

As Maurice Pérol, MD, of the Centre Léon Bérard, remarked during his discussion of these two studies, a key shortcoming of both trials is the fact that the investigational regimens were not compared against osimertinib, a third-generation *EGFR* TKI that represents a new standard of care for *EGFR*-mutated disease in many parts of the world. Acknowledging the caveats of cross-trial comparisons, Dr. Pérol deduced that in the first-line setting, adding either ramucirumab or pemetrexed/carboplatin to a first-generation TKI probably yields about the same PFS duration as osimertinib alone. However, in terms of treatment sequencing, using one of the novel regimens up front and reserving osimer-

tinib for patients with T790M-positive disease at the time of progression may lead to better survival outcomes across all lines of therapy (Fig. 2). Ultimately, the preferred first-line treatment for *EGFR*-mutated NSCLC will depend on patient characteristics, disease characteristics (eg, brain metastasis, co-occurring mutations), the tolerability profile of a given regimen, patient-reported outcomes, cost, and treatment availability, according to Dr. Pérol.

Maintenance Treatment of Metastatic NSCLC

Looking beyond first-line therapy, a randomized phase III clinical trial, ECOG-ACRIN 5508, evaluated which maintenance regimen should be the standard of care when bevacizumab is included as part of the induction regimen in patients with advanced non-squamous NSCLC (Abstract 9002). More specifically, three maintenance regimens—bevacizumab monotherapy, pemetrexed monotherapy, and bevacizumab plus pemetrexed combination

Ultimately, the preferred first-line treatment for EGFR-mutated NSCLC will depend on patient characteristics, disease characteristics (eg, brain metastasis, co-occurring mutations), the tolerability profile of a given regimen, patient-reported outcomes, cost, and treatment availability

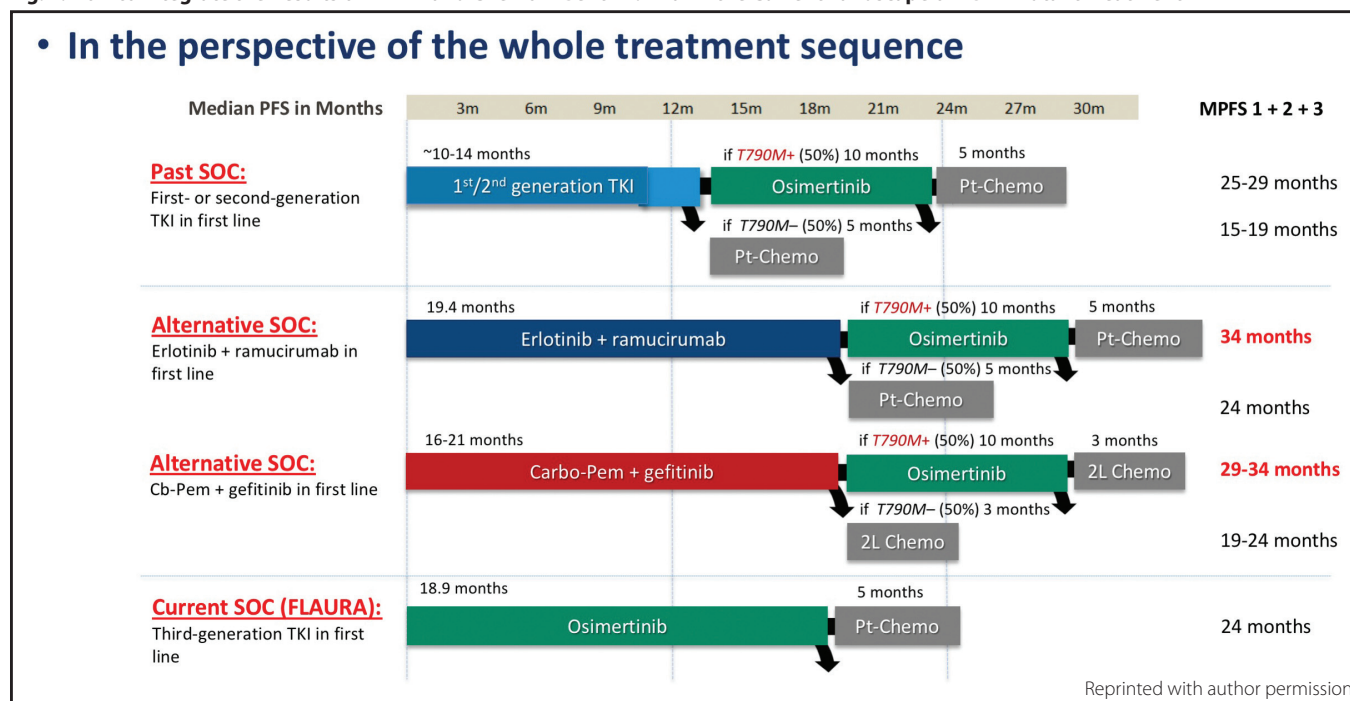
—Dr. Maurice Pérol

therapy—were compared among 1,516 patients who achieved stable disease or better following four cycles of first-line carboplatin/paclitaxel plus bevacizumab. The participants were stratified by smoking status, sex, disease stage, and response to induction therapy prior to randomization, but not by *EGFR*/*ALK* mutation status since the trial was designed in 2010 before such testing became part of routine practice.

The findings showed that the addition of pemetrexed to bevacizumab improved median PFS versus both bevacizumab monotherapy and pemetrexed monotherapy (7.5 vs 4.2 and 5.1 months, respectively; $p < 0.001$ for bevacizumab + pemetrexed vs bevacizumab monotherapy vs pemetrexed monotherapy). However, this did not translate into increased median OS (16.4 vs 14.4 and 15.9 months; $p = 0.28$ for bevacizumab + pemetrexed vs bevacizumab monotherapy), which was the primary endpoint of the trial. Combination maintenance also resulted in a higher incidence of grade 3/4 TRAEs compared with either bevacizumab or pemetrexed alone (50% vs 29% and 37%, respectively).

Given three clinical trials—ECOG-ACRIN 5508, AVAPERL,⁶ and

Fig. 2. How to Integrate the Results of RELAY and Chemo + Gefitinib Trial in the Current Landscape of *EGFR* Mutant Treatment



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COMPASS⁷—that have now failed to show an OS benefit with bevacizumab-pemetrexed maintenance therapy following prior bevacizumab-containing therapy, Dr. Pérol concluded that “we do not have any clear evidence, to date, [justifying] combination maintenance for our patients.... Pemetrexed is still the preferred maintenance option after a pemetrexed-containing induction regimen.” He noted that in situations where pemetrexed is not used up front, such as after carboplatin/paclitaxel/bevacizumab induction therapy, maintenance bevacizumab constitutes an acceptable alternative that offers a lower level of toxicity.

Novel Cytotoxic Therapy for SCLC

Tremendous unmet clinical need exists in SCLC, and yet no novel therapies have been able to top second-line topotecan. “Although topotecan leaves much to be desired with respect to both efficacy and toxicity, it is the standard of care, and no investigational agent has shown superiority in a randomized study over the past 20 years,” according to Anna F. Farago, MD, PhD, of Massachusetts General Hospital and Harvard Medical School.

Lurbinectedin, a synthetic analog of trabectedin adminis-

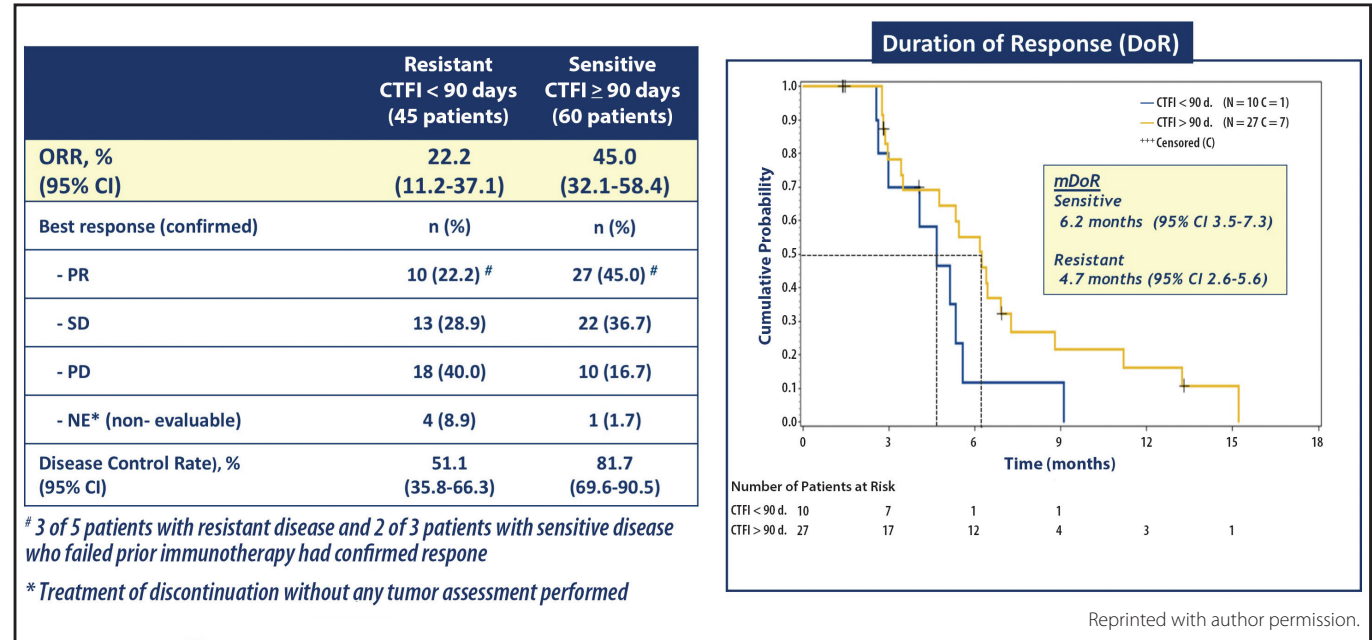
tered intravenously every 3 weeks, may prove worthy of challenging topotecan’s position. Luis Paz Ares, MD, PhD, of the Hospital Universitario, presented the results from a phase II trial of single-agent lurbinectedin conducted in patients with SCLC whose disease had progressed after one prior line of chemotherapy with or without immunotherapy (Abstract 8506).

As Dr. Paz Ares explained, SCLC is a transcription-addicted tumor driven by dysregulated expression of several key transcription factors. Lurbinectedin upsets these processes by binding to gene promoter regions, creating DNA breaks, and inhibiting transcription, ultimately downregulating the expression of growth-promoting proteins.

Among the 105 patients included in the trial, the objective response rate (ORR) to lurbinectedin was 35.2%—all partial responses—and the median duration of response was 5.3 months. Of note, 5 of 8 patients who failed prior immunotherapy demonstrated a response to lurbinectedin.

Subgroup analyses revealed that lurbinectedin conferred activity regardless of

Fig. 3. Antitumor Activity According to Sensitive or Resistant Population



whether patients had platinum-sensitive or platinum-resistant disease (Fig. 3). Moreover, about 40% of patients attained a longer PFS duration with lurbinectedin than with their first-line chemotherapy. The median PFS with lurbinectedin monotherapy was 3.9 months, and median OS was 9.3 months.

Lurbinectedin appeared to be relatively well tolerated, with a manageable safety profile. The most common all-grade

“Although topotecan leaves much to be desired with respect to both efficacy and toxicity, it is the standard of care, and no investigational agent has shown superiority in a randomized study over the past 20 years.”

—Dr. Anna F. Farago

TRAEs included fatigue (58.1%), nausea (32.4%), and decreased appetite (21.0%), the great majority of which were mild or moderate in severity. By far the most common grade 3/4 TRAE was neutropenia (22.9%). Few patients discontinued treatment due to adverse events (1.9%) or experienced treatment-related serious adverse events (10.5%), and there were no treatment-associated deaths.

“We may conclude lurbinectedin is emerging as a potential new treatment alternative for the second-line setting in [patients with] SCLC,” Dr. Paz Ares remarked.

Dr. Farago affirmed that lurbinectedin edges out topotecan based on historical efficacy data given numerically better ORR and OS findings. However, she noted that the “high OS that we see with lurbinectedin may in part reflect the activity of this drug, but may also reflect the trend that we’ve seen over time with OS improving in SCLC studies in the second-line space.”

Although lurbinectedin has received an Orphan Drug Designation by the U.S. Food and Drug Administration for the treatment of SCLC, Dr. Farago

feels it will be important to see phase III data for the agent. This will come from the global, randomized phase III ATLANTIS study that will compare lurbinectedin plus doxorubicin versus either topotecan or cyclophosphamide/doxorubicin/vincristine in patients with SCLC progression following one line of platinum-based chemotherapy (NCT02566993). ♦

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INDUSTRY AND REGULATORY NEWS

CASPIAN Trial to Report Improved OS for Durvalumab in SCLC

June 27, 2019—According to an interim analysis, the phase III CASPIAN trial (NCT03043872) of durvalumab plus etoposide and chemotherapy for previously untreated late-stage SCLC has met its primary endpoint of clinical and statistical OS improvement for durvalumab. Safety and tolerability was in line with known data for this drug.

This triple-arm, open-label, multicenter, global, randomized phase III trial was conducted in more than 200 centers in 22 countries. Eligible patients received standard etoposide/platinum-based chemotherapy, either alone or in combination with durvalumab or durvalumab and tremelimumab.

Data will be presented at the 2019 IASLC World Conference on Lung Cancer. ♦

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EVOLVING STANDARDS OF CARE

A Discussion with Dr. Shirish Gadgeel: Consolidating Gains with Chemotherapy in SCLC Maintenance Trials



Shirish Gadgeel, MBBS, is the Mary Lou Kennedy Research Professor in Thoracic Oncology and a professor in the Division of Hematology/Oncology at the University of Michigan Rogel Cancer Center. He is the co-leader of the Thoracic Oncology Research Program and associate director for cancer care at Networking and Affiliated Centers. In an interview with the *IASLC Lung Cancer News*, Dr. Gadgeel explained the purpose of maintenance trials in SCLC and the challenges of enrolling patients on clinical trials at the time of an SCLC diagnosis. He also discussed a few pivotal maintenance trials and their implications for further research and daily care.

Q: Is the maintenance setting a viable venue for drug development and exploration in SCLC?

A: As a general matter, I do think maintenance trials have value. SCLC is a unique tumor in that patients can be

very symptomatic at the time of diagnosis; therefore, systemic chemotherapy must be initiated relatively quickly. The current recommended chemotherapy regimen does, at least initially, produce responses quite quickly in a good proportion of patients; however, this benefit is not sustained in a substantial number of patients. Unfortunately, as of now, second-line therapies have not shown significant or durable benefit. Therefore, if there is a survival benefit in a maintenance trial, which is a clear and clean endpoint, there is a pretty good chance that the maintenance therapy led to the improvement.

Q: Do the positive results from IMpower133¹ make further studies of maintenance therapy problematic? Or does the overall survival (OS) advantage seen in this study re-invigorate such efforts?

A: I think that maintenance trials still have relevance despite the new positive dataset from IMpower133, in

which atezolizumab plus chemotherapy improved survival compared with chemotherapy alone. Although we see improvement, the median survival is still only a little more than 12 months, so there is further room for improvement.

IMpower133 results don't change my opinion because an improvement in survival may actually be a reason to consider other drugs in addition to maintenance atezolizumab.

Q: CheckMate 451¹ did not show an OS benefit for ipilimumab and nivolumab in combination versus placebo as maintenance therapy in extensive-stage SCLC. Please comment on the study design and objective endpoints.

A: CheckMate 451 was a pretty large trial of 800 patients that failed to meet the primary endpoint of OS. Although disappointing, I don't think the results are necessarily surprising because when you examine the existing data for checkpoint inhibitors in extensive-stage SCLC, it is clear that the drugs work but only

for a minority of patients. In that minority, however, the benefit can be sustained. It would make sense that this benefit does not translate to a very

large study population. I think that with these immunotherapy agents, particularly in SCLC, biomarkers are even more relevant. It would be interesting to see if the investigators of CheckMate 451 assessed whether patients with specific biomarkers in their tumors did derive more benefit with the combination of nivolumab and ipilimumab as maintenance therapy. Current data suggest two biomarkers that might be relevant with regard to efficacy of immunotherapy: tumor mutation burden and PD-L1 expression.

CheckMate 032³ showed that the ben-



Dr. Shirish Gadgeel

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ments bowing to political pressure) and more importantly patient well-being can suffer. The latter is often both literal and figurative with both an actual and perceived lack of access to treatment.

There is also variation in cost. "List-price" cost is not reflected in actual cost negotiated by the public system or with insurance companies or private hospital groups. In the case of patients who pay for their own medications, certain agents are sometimes offered at a discounted rate when compared with the "list-price" value. This information is not readily available in the public domain.

Using Challenges to Spark Enthusiasm, Partnership

Because of these increasingly lengthy roads to insurance-funded treatment and the impressive scientific strides made within the field, enthusiasm for participation in lung cancer research studies has increased. Up until relatively recently, thoracic oncology patients in Ireland had no or limited access to novel therapeutics through clinical trial participation. During the past several years, significant effort has been expended into lung cancer clinical research programs in Ireland.



Established in 1996, Cancer Trials Ireland (CTI) is the leading clinical trials organization in Ireland, and with cooperation from industry, it has coordinated much of this effort. It provides a range of cancer trial functions including planning, opening, co-coordinating, supporting, monitoring, and auditing of trials to facilitate the important work of researchers in Ireland but also to extend involvement to other European countries. In this regard, CTI has often acted as a trial sponsor.

More recently, between 2014 and 2018, lung cancer trial accrual in Ireland has doubled from very humble beginnings. Treatment trials have recruited between 40 and 75 patients per year, with many more participating in translational research studies. This growth has been achieved despite the absence

of direct investment and even a 20% budgetary cut to the funding of a cancer research infrastructure during this period in Ireland, and so our hope is that this fledgling group will continue to grow. Patients, investigators, and research teams in Ireland have participated in some of the most highly cited and practice-changing industry-sponsored studies including KEYNOTE-024, KEYNOTE-189, CheckMate 227, and CheckMate 451. Collaborations with cooperative groups include European Thoracic Oncology Platform-sponsored trials such as BELIEF, EMPHASIS-lung, and SPLENDOUR, and patients in Ireland have also participated in the ECOG 1505 adjuvant study.

The lung cancer trials portfolio includes radiotherapy, translational, basket, and investigational medicinal product studies in both NSCLC and SCLC, ranging from local to advanced metastatic disease. These trials offer treatment options not otherwise available to thoracic oncology patients in Ireland through other channels, such as licensed treatments or compassionate-access programs.

As of January 2019, there were nine open lung cancer trials, an additional nine trials in the feasibility and set-up stages, and another 10 trials in the follow-up or close-out phases.

As researchers, physicians, care teams, and patient advocates working together for lung cancer care in Ireland, we are hopeful that drug access and equity of care for our patients will continue to improve, facilitated by our striving for clinical excellence through research. ♦

Acknowledgments to Vincent O'Mahony (Project Manager Cancer Trials Ireland) and Dr. Hazel O'Sullivan (Specialist Registrar, ICHMT).

About the Author: Dr. Coate is a consultant medical oncologist and an assistant professor in Medicine at the University Hospital Limerick. She chairs the Lung Cancer Clinical Trials Group for Cancer Trials Ireland. You can follow her on Twitter @lindacoate. Dr. O'Sullivan is Medical Oncologist Specialist Registrar at Mater Misericordiae University Hospital, Dublin, Ireland.

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SCLC Maintenance Trial

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efit from immunotherapy agents, particularly the combination of nivolumab and ipilimumab, was restricted to patients who had high tumor mutation burden. Likewise, patients with PD-L1-positive tumors appeared to derive benefit in a phase II trial of pembrolizumab. Of note, PD-L1 expression was not only assessed within tumor cells but also in stromal cells, such as tumor-associated macrophages or tumor-associated lymphocytes, so positivity was based on a composite score for PD-L1 expression in the tumor and in the surrounding microenvironment. If the tumor had positive PD-L1 expression, then patients appeared to do well on the treatment. I think that a maintenance trial evaluating these checkpoint inhibitors, but restricted to patients with these biomarkers, may show a survival advantage.

Q: What are your thoughts on the ongoing MERU trial (NCT03033511) testing rovalpituzumab tesirine (Rova-T) in this setting? Given the track record in TRINITY,⁴ are there concerns regarding toxicity?

A: Based on the available data—particularly the TRINITY trial—and some personal experience, I continue to have some concerns about the toxicity of Rova-T. All of the toxicities associated with the agent are manageable, but my concern is that the toxicities can be sustained and could potentially affect the ability to initiate subsequent therapies. Even if the drug does wind up providing clinical benefit, my concern is that when disease eventually progresses, patients will have a more difficult time tolerating the next treatment because of the toxicities they experienced receiving Rova-T. However, I am awaiting the results of MERU before making a final decision about the clinical value of this drug in the maintenance setting. ♦

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Special Session to Honor Dr. Adi Gazdar

By Ignacio Wistuba, MD, and John Minna, MD

Dr. Adi Gazdar was a scientific pioneer, a groundbreaking pathologist, a loyal friend, and an inspiring mentor.

Dr. Gazdar was born in India; he earned his medical degree from Guy's Hospital Medical School at the University of London and completed residencies in pathology at Peter Bent Brigham Hospital and New England Deaconess Hospital in Boston before joining the National Cancer Institute (NCI) in 1968. During his remarkable 5-decade career, Dr. Gazdar served 23 years with the NCI as a senior scientist and section head. His NCI experience included initially leading its Viral Pathology Section; the Human Tumor Cell Biology Laboratory for the NCI's VA Medical Oncology Branch from 1975 to 1981; and then the Human Tumor Cell Biology Section for the NCI-Navy Oncology Branch from 1981 to 1991. His team collected, cataloged, and analyzed thousands of human cancer speci-

in Molecular Oncology Research, and deputy director of the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research.

Dr. Gazdar's efforts in the laboratory yielded the first large panel lung and breast cancer cell lines, used by investigators around the world, and he developed molecular methods for detecting early lung tumors. Dr. Gazdar also identified several genes involved in the pathogenesis of different cancers. In lung cancer, he uncovered mutated genes dysregulated by mutation and DNA methylation, provided some of the first work characterizing neuroendocrine cancers, such as SCLC, and played a major role in the discovery of the mutated epidermal growth factor receptor (EGFR) gene as a therapeutic target in lung cancer. During his long career, Dr. Gazdar published approximately 800 articles, book chapters, and commentaries, and has been cited more than 110,000 times, ranking him among the top 1% of scientists in the biomedical field. His numerous honors and recognitions include a 2004 award from the prestigious Jacqueline Seroussi



Drs. John D. Minna (left) and Adi F. Gazdar (1993).



Dr. Adi Gazdar was a remarkable mentor and friend. His insight into tumor biology was unique, and his contribution to the study of lung cancer biology was remarkable. Dr. Gazdar was, by nature, very modest, and I think that he would have been very proud of this session honoring his scientific achievements.

—Dr. Fred Hirsch

mens with an emphasis on lung cancer and lymphomas. In 1991, he joined his long-time colleague Dr. John D. Minna at the University of Texas Southwestern Medical Center, Dallas, Texas, where he had a distinguished 27-year career as professor of pathology as the W. Ray Wallace Distinguished Chair

Memorial Foundation for Cancer Research in Israel and the 2003 Mary J. Matthews Pathology/Translational Research from the IASLC.

Dr. Gazdar was an inspirational role model for many young scientists, mentoring over 100 post-doctoral fellows from around the world. IASLC established the Adi Gazdar Translational Research Fellowship Award in 2017 to honor his legacy in lung cancer training.

A special symposium to honor Dr. Gazdar's legacy will be held at the IASLC 2019 World Conference on Lung Cancer on Saturday, September 7, 17:30-19:00. The symposium is co-chaired by Drs. Fred Hirsch, Tetsuya Mitsudomi, and Ignacio I. Wistuba. The speakers will address Dr. Gazdar's outstanding qualities as mentor (Tetsuya Mitsudomi, MD) and friend (Fred Hirsch, MD, PhD), as well as his legacy in cancer research (Peter Ujhazy, PhD), including his impact of cell line development (Paul Bunn, MD), his research on lung premalignancy (Kwun Fong, MD, PhD), and his role in understanding the evolution of SCLC and neuroendocrine tumors (Lauren Byers, MD). ♦

INDUSTRY AND REGULATORY NEWS

A Drug for an Undruggable Target

A novel small-molecule inhibitor targeting KRAS, known as AMG 510, demonstrated a 50% response rate in patients with NSCLC who had *KRAS*^{G12C} mutations, which are found in approximately 13% of lung adenocarcinomas and up to 3% of other solid tumors. Initial safety and response data from a first-in-human, open-label, phase I trial of this novel small-molecule KRAS inhibitor were presented at the 2019 American Society of Clinical Oncology (ASCO) Annual Meeting (NCT03600883) and found the agent to be well tolerated.

All patients in phase I had a *KRAS*^{G12C} mutation confirmed by DNA sequencing. Eligible patients had measurable or evaluable disease, an ECOG PS ≤ 2, and a life expectancy of > 3 months. Patients with brain metastases and myocardial infarction within 6 months were excluded.

In the initial cohort of six patients with NSCLC, 15 with colorectal cancer, and one other, 10 discrete grade 1 or 2 treatment-related adverse events (TRAEs) were reported in five patients; there were no dose-limiting toxicities. In an update at ASCO, of 10 patients with advanced NSCLC and *KRAS*^{G12C} mutations, five registered a partial response. Twenty patients of the initial 22 are continuing treatment; maximum-tolerated dose has yet to be established. ♦

EVOLVING STANDARDS OF CARE

Making Headway with Lorlatinib: Q&A with Dr. Todd Bauer

Q&A

Lorlatinib, a small-molecule inhibitor of ALK and ROS1, was granted accelerated U.S. Food and Drug Administration approval in November 2018 for patients with ALK-positive metastatic NSCLC whose disease has progressed on crizotinib and at least one other ALK inhibitor or whose disease has progressed on alectinib or ceritinib as the first ALK inhibitor therapy for metastatic disease. Todd M. Bauer, MD, a medical oncologist and senior investigator at Sarah Cannon Research Institute/Tennessee Oncology, PLLC, in Nashville, has been very involved with the development of lorlatinib since the beginning. In the following interview, Dr. Bauer discusses some of lorlatinib's unique toxicities, as well as his first-hand experiences with the drug.

Q: Lorlatinib's toxicities, including CNS effects and secondary elevations of cholesterol and triglycerides, are unique. To what extent do these side effects influence tolerability, and what are the best tips for managing toxicities?

A: I have one of the longest-running patients in the world. He was amongst the first patients ever treated when he started dosing in April of 2014, and has tolerated it quite well for over 5 years. He has had a near-complete response, with just a few 5- or 6-mm spots from prior CNS metastases that were irradiated, which I view as mostly just scar tissue

and not a sign of active disease.

The CNS effects that we've seen with lorlatinib are interesting—they are a little tough to put a finger on. When we first started using lorlatinib and were escalating the doses, we had some reports of sluggish thought. Patients would indicate that they just couldn't quite connect the dots—almost what you might think “chemo brain” would be like. This is something we had not seen previously with the ALK TKIs, so it became a point of focus. There are also some effects regarding mood (patients reporting depression and generally feeling poorly) and others regarding speech. For the vast majority of patients, we were able to stop therapy, and then the symptoms would resolve. We would then reduce the dose as necessary, and patients were able to continue on without problems.

Regarding cholesterol and triglycerides, most of the patients are very compliant with a statin and a fibrate as necessary. I had one patient who did not want to pursue pharmacologic therapy; he just wanted to manage it through diet. Finally when his cholesterol rose to the 500s, he relented and let me start him on a statin. People do well with the statins, which control cholesterol without any major



Dr. Todd M. Bauer

problems. So the correlation between lorlatinib and elevated cholesterol is there, it's very real—I can't tell you why it happens, but it is very controllable using a statin and/or a fibrate as necessary.

Q: What are your best-practice tips for this fairly new drug?

A: The key to lorlatinib is that it is a very different TKI from crizotinib, for example, which caused a lot of edema and other significant issues for patients. It's really a matter of watching the labs closely and talking to the patient to ensure that his/her thought processes are okay, and that there are not any mood changes. It is important to incorporate the family and caregivers into that discussion as well because they can sometimes identify subtle shifts that patients have trouble identifying themselves.

It's amazing the number of times, especially on a clinical trial, that a patient will “shush” their loved one and tell them not to bring something up because the patient is worried that he/she will be taken off the drug. Caregivers are the key to really understanding some toxicities that the patients sometimes minimize or do not want to acknowledge.

Q: How does lorlatinib compare to alectinib or brigatinib?

A: I think it compares very well to those drugs. We don't have any direct head-to-head comparison but certainly the intracranial control rate that we see with lorlatinib, even after failure of alectinib or

brigatinib, is hopeful; it can re-establish control of disease that has progressed with those two drugs. Those are great drugs; I just think that, if you look at the basic science, lorlatinib targets the resistance mutations within ALK a bit more strongly than either alectinib or brigatinib. So lorlatinib can be a salvage medication for patients whose disease progresses on those therapies.

Q: What is in the pipeline for lorlatinib?

A: I think that there will continue to be studies looking at how to best sequence these drugs. We truly don't know that answer right now. I think it is safe to say that crizotinib has fallen out of use after the presentation of the ALEX data, with alectinib now being the first-line drug. Second line gets a little fuzzy, so trials will be important.

It's an exciting time for patients with ALK fusion-positive lung cancer. The drugs available now are incredible, but we always encourage—in the appropriate setting—participation in clinical trials to help better define patient care. ♦

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EVOLVING STANDARDS OF CARE

JAVELIN Lung 200: Potential Reasons for Avelumab's Failure to Provide OS Benefit

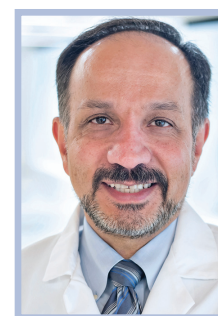
By Hossein Borghaei, DO, MS

In 2015, the use of checkpoint inhibitors in the second-line setting for metastatic lung cancer became the standard of care with the approval first of nivolumab followed by pembrolizumab and later atezolizumab. In all randomized trials with these agents, the comparator arm was docetaxel because it represented the standard-of-care post-therapy with a platinum-based chemotherapy doublet at that time. Clearly, we have observed a substantial shift in the use of these drugs in metastatic lung cancer, with recent trials showing a significant advantage for the combination of chemotherapy and immunotherapy as frontline treatment compared to platinum-based chemotherapy alone. This approach is now

the standard of care in the United States and most parts of Western Europe; at this point, in the absence of an oncogenic driver, the majority of patients with newly diagnosed metastatic lung cancer, regardless of histology, receive a platinum-based chemotherapy doublet plus a checkpoint inhibitor upfront.

JAVELIN Lung 200 was a randomized phase III trial designed to test the efficacy of avelumab versus docetaxel in patients with metastatic NSCLC after progression on standard platinum-doublet chemotherapy.¹ This multinational study, conducted in 31 countries, did not meet its primary endpoint in the intent-to-treat patient population. The eligibility requirements were standard for a trial of this nature. Overall, 792 patients were enrolled and randomly

assigned to the two arms. PD-L1 status was positive in approximately 67% of patients in either arm. The median overall survival was not different in this group of patients, at 11.4 months for avelumab and 10.3 months for docetaxel. In a prespecified exploratory analysis, patients with higher PD-L1 expression (50% and 80%) receiving avelumab had, in fact, better median survivals compared to those receiving docetaxel. As reported, toxicities with avelumab were fairly consistent with those observed with other



Dr. Hossein Borghaei

checkpoint inhibitors, with the possible exception of infusion-related reactions, which occurred in approximately 17% of patients treated with avelumab.

One Checkpoint Inhibitor May Not Be the Same as Another

There are several possible explanations for why avelumab failed to meet expectations. Overall survival is affected by subsequent therapies. In the PD-L1-positive group, 48% of patients in the docetaxel arm received post-study treatment, of whom 26% had some form of immunotherapy with a checkpoint inhibitor. This constitutes a higher rate of post-progression use of a checkpoint inhibitor than prior studies. This makes sense because these active agents are now avail-

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GLOBAL INITIATIVE

Korean Lung Cancer Screening Project (K-LUCAS) Led to Launch of New National Lung Cancer Screening Program in Korea

By Yeol Kim, MD, MPH, PhD, and Choon-Taek Lee, MD, PhD

Lung cancer is the leading cause of cancer death worldwide and also in South Korea. Besides avoiding smoking, it is widely accepted that lung cancer screening is possibly the most effective way to reduce lung cancer mortality; however, researchers have only recently provided scientific evidence to support this strategy. In 2011, The National Lung Screening Trial in the United States showed that screening with low-dose computed tomography (CT) targeted to high-risk smokers reduced lung cancer mortality by 20% compared to a control group who received general chest x-rays. More recently, in 2018, a Dutch-Belgian trial (NELSON) also yielded similar results supporting the reduction of mortality.

Based on previous studies, we started the Korean Lung Cancer Screening Project (K-LUCAS) in 2017 to evaluate the feasibility of implementing a population-based lung cancer screening program with the intent to reduce lung cancer mortality rates in South Korea.¹ K-LUCAS is the first Asian population-based, nationwide, multicenter prospective lung cancer screening trial. A total of 13,692 people participated in K-LUCAS, which involved 14 hospitals in Korea. The results were promising. The proportion of early-stage lung cancer detection was three times higher in K-LUCAS than the total early-stage lung cancer cases in the national cancer registry.

Ingredients for Success

Lung cancer screening is only recommended for high-risk populations

because the harm from participating in lung cancer screening (e.g., exposure to radiation and complications during diagnosis procedures) can be greater than the benefit (e.g., early detection of lung cancer) in low-risk nontarget populations. K-LUCAS also examined the feasibility of selecting appropriate participants based on questionnaires provided by national health screening programs or in smoking cessation clinics. Those questionnaires include questions on current smoking status, smoking history, medical history, and demographics. Questionnaire-based participant selection was evaluated to be an appropriate method in K-LUCAS.

The Korean National Cancer Screening Program (KNCS) provided a regular cancer screening service for five major cancers (stomach, colon, breast, cervix, and liver), when people come to a certain age. KNCS will now be expanded to include lung cancer screening.



Another key characteristic of K-LUCAS was the implementation of a network-based diagnosis-supporting system using a computer-aided detection program that aimed to improve nodule detection sensitivity and minimize diagnostic errors. The network-based diagnosis-supporting system was implemented to provide a diagnostic aid for general radiologists

to improve quality control and for chest specialists to reduce their reading time. The screening results were standardized by the lung imaging reporting and data system (Lung-RADS) proposed by the American College of Radiology.² The implementation of the network-based diagnosis-supporting system in K-LUCAS was also effective in keeping the specificity comparatively high while increasing the sensitivity of the screenings.

Finally, K-LUCAS provided mandatory smoking-cessation counseling to all currently smoking participants, as the negative results from lung cancer screening might have provided false reassurance to smokers to continue smoking.

Based on these promising results of K-LUCAS, the government of South Korea has decided to introduce a population-based lung cancer screening program beginning in July 2019.

Details of Implementation

The Korean National Cancer Screening Program (KNCS) provided a regular

cancer screening service for five major cancers (stomach, colon, breast, cervix, and liver), when people come to a certain age. KNCS will now be expanded to include lung cancer screening. The National Health Insurance Service (NHIS) in Korea supports 90% of the cost of KNCS as a part of the national social security system.

The national lung cancer program will send invitation letters to screening candidates who are current smokers between the ages of 54 and 74 with at least 30 pack-years of smoking history as reported on the questionnaires submitted in other national health screening programs. The screening interval will be 2 years. Within 2 years, the program plans to expand to ex-smokers with over 30 pack-year exposures. The low-dose CT screening cost per person will be approximately U.S. \$100. The examinee will pay only 10% of the cost. Moreover, the lower 50% income group can undergo the lung cancer screening for free.

High-quality screening units throughout the country will be designated for the program based on the facility's availability of CT with at least 16 channels, certified radiologists with credit for lung nodule evaluation, and physicians who can provide professional counseling for screening results. A web-based program will be available for certified screening units to support the diagnosis and to monitor the quality of the screening.

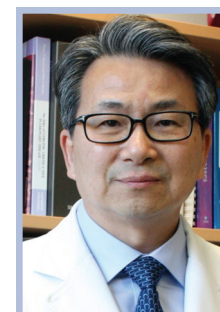
Challenges and Potential Next Steps

Most people and doctors are delighted to hear about the announcement of lung cancer screening; however, there have been already some disagreements regarding the implementation of this program that must be addressed.

First, many clinics argue that the criteria to qualify as a certified screening center are too strict. Second, concerns have been raised by pulmonologists and



Dr. Yeol Kim



Dr. Choon-Taek Lee

INDUSTRY AND REGULATORY NEWS

Device Becomes Second Approved Therapy for Unresectable MPM

A new device was approved by the U.S. Food and Drug Administration (FDA) on May 23, 2019, for use in the first-line setting for treatment of unresectable, locally advanced or metastatic malignant pleural mesothelioma (MPM). This is the first therapeutic approval in 15 years for MPM.

NovoTTF-100L is a tumor-treating fields (TTF) device, which uses electric fields to disrupt solid tumor cancer cell division. The device is approved for use in combination with pemetrexed plus a platinum-based chemotherapy—pemetrexed plus cisplatin being the only approved therapy for patients with unresectable MPM. In an effort to promote therapeutic innovation for rare diseases, the Humanitarian Device Exemption—the approval path for the NovoTTF-100L—does not require evidence of efficacy. However, data from the STELLAR trial, a prospective, single-arm trial of NovoTTF-100L plus chemotherapy in 80 patients with unresectable MPM showed no serious systemic adverse events for the device, with mild-to-moderate skin irritation being the most common adverse event. Of the 53 patients with epithelioid MPM, median OS was 21.2 months; median OS was 12.1 months for the 21 patients with non-epithelioid MPM. At 12 months, 62% of all patients were alive, and the ORR was 40%. The median PFS was 7.6 months. Further studies are needed to determine the efficacy of this device. Until phase III data are available to document superiority compared with chemotherapy alone, it is unclear how readily this device will be embraced in the United States or elsewhere. ♦

MEETING PREVIEW

First School of Nursing To Be Held at 2019 Latin American Conference on Lung Cancer

By Enza Esposito Nguyen, DNP, RN,
ANP-BC, AOCNP

The upcoming ninth Latin American Conference on Lung Cancer—to be held in Mexico City, Mexico, in October 2019, and sponsored by the IASLC Latin American Group (LATAM)—will feature, for the first time, a notable, overdue addition: the first School of Nursing at a regional meeting.

This intense, 1-day workshop is aimed to support and foster the emerging role of the thoracic oncology nurse in Latin America and will be held on October 17, 2019. A panel of nurses, nurse practitioners, physicians, physical therapists, and researchers from the United States and Latin America will discuss topics such as the role of the nurse in clinical trials, lung cancer screening programs, multidisciplinary management of patients receiving immunotherapy, and palliative care in thoracic malignancies. As a Latino nurse who was trained and who has worked

in the United States for the past 22 years, I think the time is perfect to encourage and give my nursing colleagues throughout Latin America the tools and confidence to play a more dynamic role in thoracic oncology.

This innovative idea was the vision of Luis Raez, MD, FACP, FCCP, and



Dr. Enza Esposito
Nguyen



“We are very happy to have an activity this year involving nurses from all over Latin America, continuing the great contribution that nurses have made over the past few years in IASLC and incorporating new members into the big IALSC family.”

– Dr. Christian Rolfo

Christian Rolfo, MD, PhD, MBA, who approached me just before 2018 World Conference on Lung Cancer, pointing out growing gap that is often unnoticed: the need to arm nurses outside of the United States with the tools and knowledge to become important members of the multidisciplinary thoracic oncology team. Nurses and nurse practitioners in the United States have become a vital part of the team by participating in screening programs, enrolling patients onto clinical trials, managing treatment-related adverse events, dynamically participating in tumor boards, and, in the case of the nurse practitioner and some physician assistants, autonomously managing patients’ treatments in collaboration with the oncologist.

Today’s treatments are far more complex than they were in the past, and

require not only the expertise of the physician, but of a whole professional team including nurses, therapists, dieticians, and social workers, to best manage the physical, social, and psychological sequelae of complicated and lengthy treatments. Our patients are living longer thanks to the great amount of progress made just in the past decade, and it literally requires a village to care for these patients.

The aim of the School of Nursing at the LATAM meeting is to provide an invitation “to the table” for nurses and advance practice nurses. I believe strongly there is a lot we can learn from each other; elevating the skills of nurses throughout Latin America as well as other parts of the world will advance both patient care and the IASLC’s mission.

Dr. Luis E. Raez, IASLC-LATAM chair, noted what an important opportunity this

meeting is for nurses and nurse practitioners (APRNs) based in Latin America. In addition to this 1-day event held specifically for and taught by APRNs, attendees will have the benefit of gaining a broader understanding of the latest developments in lung cancer. The School of Nursing content will feature evidence-based instruction regarding management of targeted and immunotherapy complications, as well as provide best practices for ambulatory challenges, pain management, and palliative care initiatives. “We praise the efforts of Dr. Nguyen and her team for putting together such an important event,” Dr. Raez said.

According to Dr. Christian Rolfo, educational chair and schools LATAM chairman, the incorporation of the nursing school in the Latin American Congress is responding to the first aim of IALSC education. “We are very happy to have an activity this year involving nurses from all over Latin America, continuing the great contribution that nurses have made over the past few years in IASLC and incorporating new members into the big IALSC family,” Dr. Rolfo said. ♦

About the Author: Dr. Nguyen is a thoracic oncology nurse practitioner, urologic oncology nurse practitioner, and doctor of nursing practice in Austin, Texas. Dr. Raez, current chairman of the IASLC Latin American (LATAM) group, is a medical oncologist who works as medical director of Memorial Cancer Institute/Memorial Health Care System in Miami-Florida, he is also clinical professor of Medicine at Florida International University (FIU) and scientific chair of the 2019 IASLC-LALCA meeting.

JAVELIN Lung 200

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able in most regions of the world, and patients have better access to potentially active drugs. Is this number enough to have changed the outcome of the trial? Because I am not a statistician, I cannot comment on this any further, but one can certainly speculate.

Study Design

Is it possible that avelumab was somehow less effective as a checkpoint inhibitor? This issue of whether there is a superior checkpoint inhibitor has been debated by many in the field, but there is no clear answer. Certainly, the number of positive trials with pembrolizumab, either alone or in combination with standard chemotherapy, makes one wonder if there is a

superior checkpoint inhibitor. However, I believe that better patient selection, better-designed studies, and clearly defined biomarker endpoints are more likely to be the reason for the success of these trials rather than the nature of the drug itself. Of note, a recent unconfirmed report suggesting that the rate of antidrug antibodies, which tend to be neutralizing, are different among the checkpoint inhibitors could provide an explanation for the different results we have been seeing. This must be investigated further.

Patient Selection

Patient selection could have been a factor in this trial. In the avelumab arm of the trial, approximately 10% of participants had brain metastasis at baseline compared with 8% in the docetaxel arm. This patient population generally has a worse

outcome. In isolation, this factor by itself is not likely to have resulted in the lack of a survival benefit, but it is conceivable that in combination with other factors, it could have been a contributing factor.

PD-L1 Expression Status

PD-L1 testing in this trial was conducted using the 73-10 pharmDx antibody. The Blueprint 2 analysis shows that this antibody is a high-quality assay that stains more PD-L1-positive tumor cells, and the 80% or higher PD-L1 cutoff with this antibody has high concordance with the 50% or higher cutoff for the 22C3 antibody used in the pembrolizumab trials. Thus, it is unlikely that biomarker testing is responsible for the results observed.

Ultimately, it is difficult to ascertain why this study did not succeed where others have. The real reasons are prob-

ably multifactorial. Certainly, other studies with avelumab are ongoing, and this drug appears to be as effective as others in this class. Occasionally, a trial fails unexpectedly. Sometimes a clear explanation is evident, but in many cases, the answer remains elusive. The negative results of the JAVELIN trial appear to be a case of the latter. ♦

About the Author: Dr. Borghaei is chief of the Division of Thoracic Medical Oncology, professor in the Department of Hematology/Oncology, co-director of the Immune Monitoring Facility, and Gloria and Edmund M. Dunn Chair in Thoracic Oncology at Fox Chase Cancer Center.

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IMMUNOTHERAPY

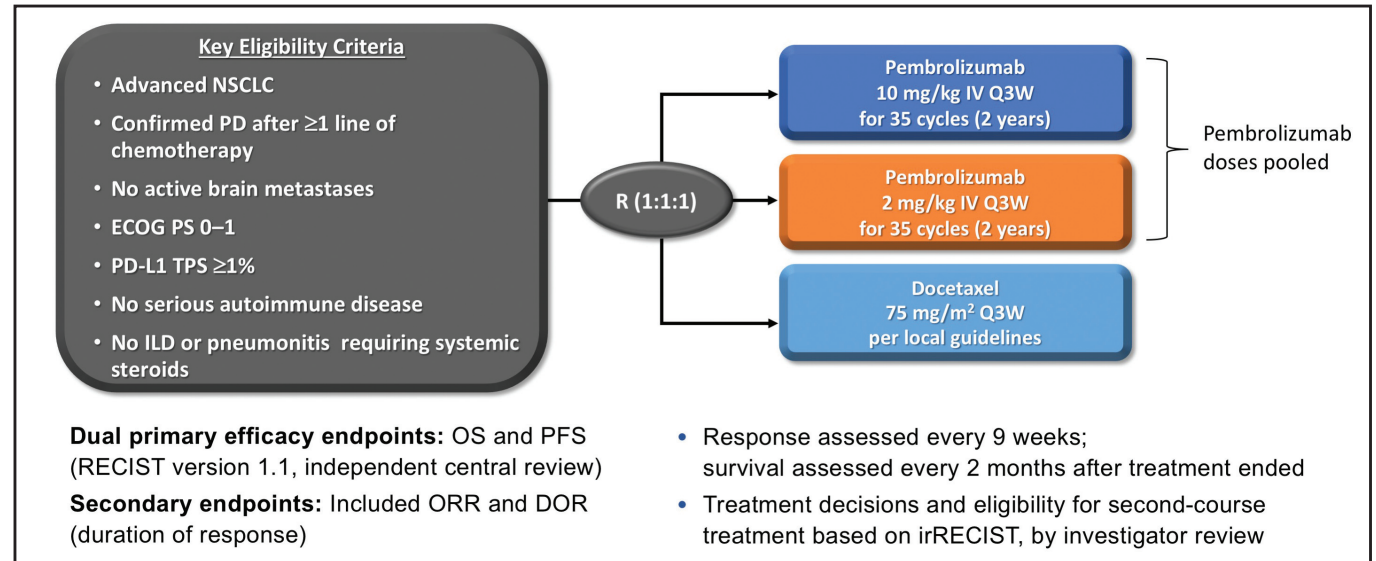
KEYNOTE-010: Long-Term Outcomes and Results of Retreatment

By Emily F. Collier, MD; Roy S. Herbst, MD, PhD; and Sarah B. Goldberg, MD, MPH

KEYNOTE-010 is an open-label phase II/III study that compared pembrolizumab (2 mg/kg or 10 mg/kg every 3 weeks) with docetaxel in previously treated patients with advanced NSCLC with a PD-L1 tumor proportion score (TPS) of 1% or higher (Fig. 1). Treatment was continued for up to 35 cycles (approximately 2 years), with the option of retreatment with a second course of pembrolizumab at progression. Primary endpoints were overall survival (OS) and progression-free survival (PFS), with secondary endpoints of overall response rate and duration of response. The results from the initial analysis were published in *The Lancet* in 2016 and demonstrated significant improvement in OS at a median follow-up of 13 months, with a median OS of 12.7 months for pembrolizumab versus 8.5 months for docetaxel (HR 0.61; $p < 0.0001$).¹ This led to the U.S. Food and Drug Administration approval of pembrolizumab in patients with previously treated metastatic NSCLC whose tumors express PD-L1 (TPS $\geq 1\%$).

The results from KEYNOTE-010 were part of a therapeutic revolution in the management of NSCLC and spurred the nearly universal adaptation of immunotherapy as second-line treatment for this disease. Similar results with other PD-1/PD-L1 checkpoint inhibitors such as nivolumab^{2,3} and atezolizumab⁴ cemented the role of immunotherapy in the treatment of NSCLC. The KEYNOTE-010 study was also the first published phase III trial data to demonstrate the utility of selecting patients based on tumor's PD-L1 expression status.¹

Fig. 1. Schema of KEYNOTE-010 (NCT01905657)



Current Data

Updated results of KEYNOTE-010 were presented at the European Society for Medical Oncology 2018 Congress.⁵ Consistent with the previously reported final analysis,¹ the updated efficacy and safety results from KEYNOTE-010 (with median follow-up of 42.6 months) confirm that pembrolizumab monotherapy provides a clinically meaningful survival benefit compared with docetaxel as a second-line treatment in PD-L1 positive (TPS $\geq 1\%$) NSCLC (Fig. 2). In the overall population of patients with NSCLC with TPS of 1% or higher, there was a median OS of 11.8 months in the pembrolizumab group versus 8.4 months in the group treated with docetaxel (HR 0.69; $p < 0.00001$). The OS benefit was even greater in patients with NSCLC with TPS of 50% or higher, with a substantially longer median OS of 16.9 months with pembrolizumab compared with 8.2 months for docetaxel (HR 0.53; $p < 0.00001$). The safety profile of pembro-

lizumab monotherapy in this study was consistent with the previously reported final analysis. Although the duration of exposure was longer for patients treated

treatment with pembrolizumab monotherapy was associated with improved health-related quality of life as compared with docetaxel.⁶



Dr. Emily F. Collier

Dr. Roy S. Herbst

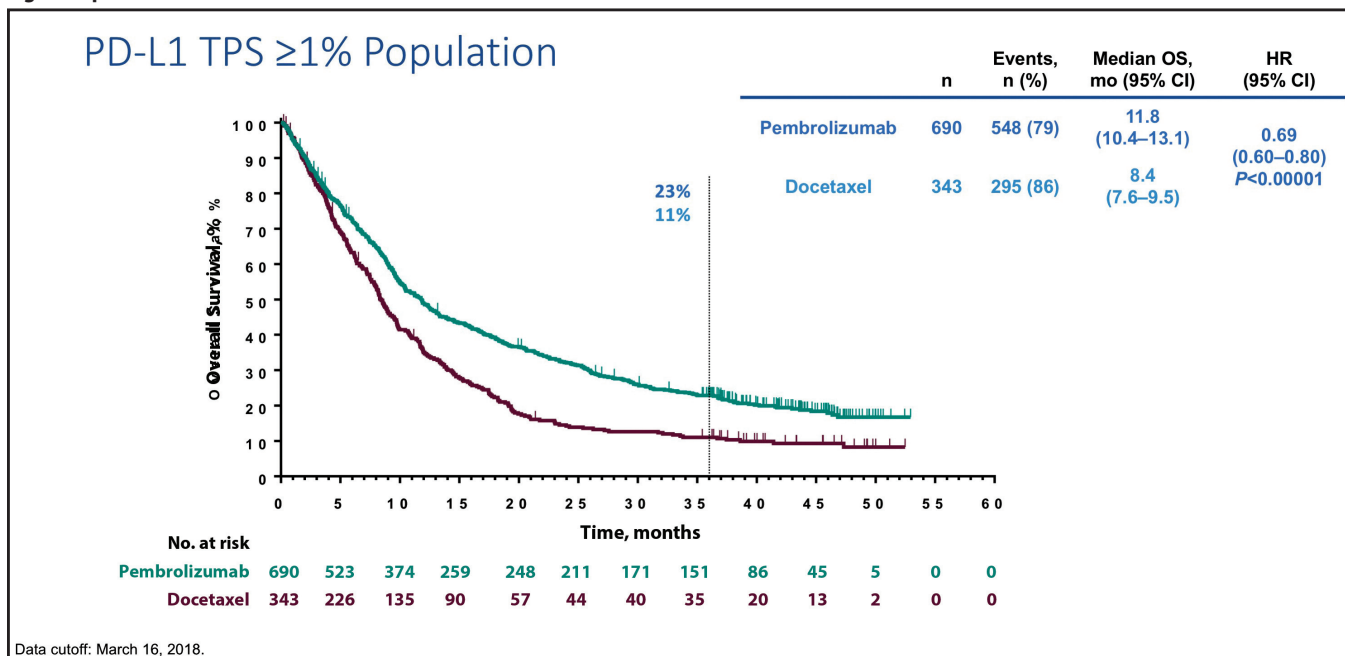
Dr. Sarah B. Goldberg

with pembrolizumab, there were still fewer grade 3 to 5 treatment-related adverse events, occurring in only 16% of the pembrolizumab group compared with 37% in the docetaxel group. Unsurprisingly, a recent publication in the *Journal of Thoracic Oncology* that used data from this trial demonstrated that in addition to prolonged survival,

Finding the Optimal Duration of Treatment

The updated information from KEYNOTE-010 also provides additional insight into an ongoing question: What is the optimal duration of treatment with checkpoint inhibitors? There is still little consensus regarding this issue in patients with NSCLC and other malignancies. For melanoma, updated results of KEYNOTE-006 demonstrated that among patients treated for 2 years, the majority (86%) had ongoing response after 20 months of observation, and of those who had disease progression, the majority responded to retreatment.⁷ CheckMate 153 evaluated continuous treatment versus 1-year fixed-duration treatment with nivolumab in patients with advanced NSCLC. Preliminary results suggested that continuous treatment beyond 1 year was beneficial, with improved PFS (HR 0.42) and a trend toward improved OS.⁸ These observations suggest that cessation at 1 year is too early. However, the question remains whether patients could potentially stop after a longer treatment duration, or if treatment should be continued as long

Fig. 2. Kaplan-Meier Estimates of OS



KEYNOTE-010

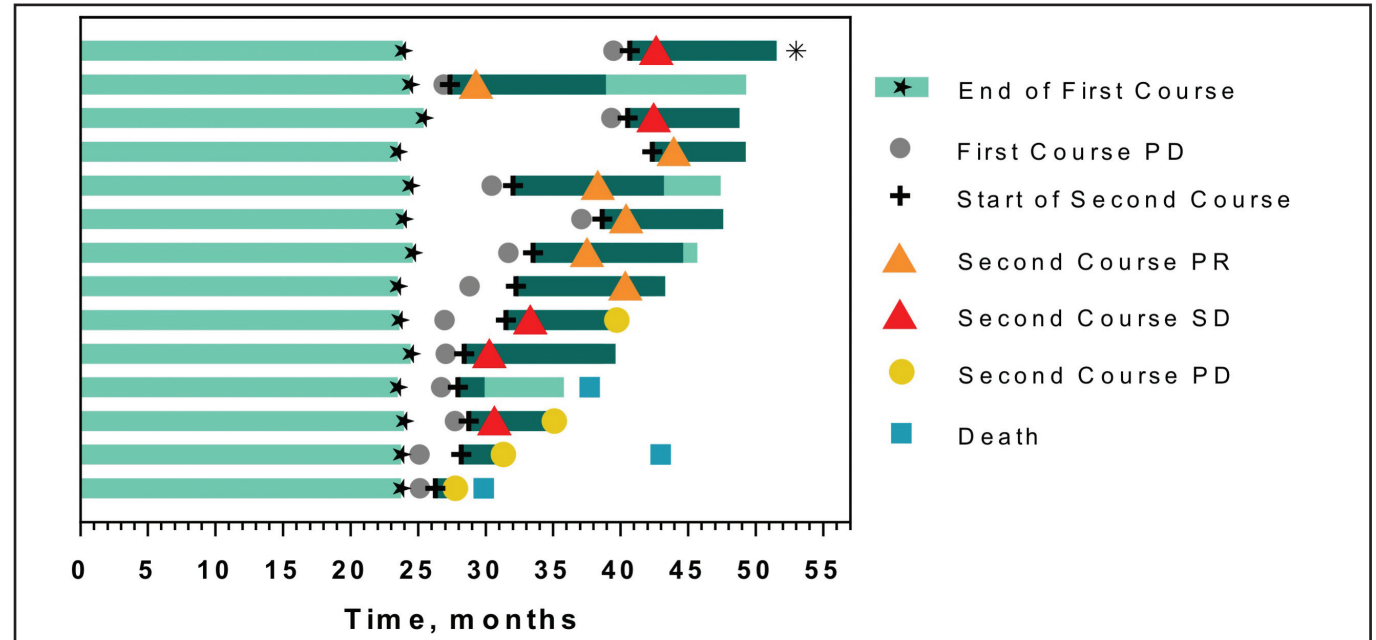
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as the drug is tolerated.

The updated results from KEYNOTE-010 may give support to the idea of a 2-year course of treatment. Of the 79 patients who completed 35 cycles (~2 years) of treatment, 26 (32.9%) had a PFS event after completing the 2 years, with a 36-month PFS rate of 70.3%. Fourteen patients went on to get a second course of pembrolizumab after progression following the initial 35 cycles of treatment. Of these 14 patients, six had a partial response, and five had stable disease during second treatment course; all 11 who responded or had stable disease were alive at the time of analysis (Fig. 3). These results are among the first from a prospective trial showing the outcome of retreatment with a checkpoint inhibitor in NSCLC. The substantial percentage of patients with ongoing responses following treatment cessation and the observation that the majority of retreated patients achieved either stable disease or partial response suggests that stopping treatment at 2 years may be reasonable. However, this is based on a small number of patients, and there is no long-term follow-up on the retreatment cohort; as such, it is premature to conclude that this is the best strategy. Additional study, ideally a prospective trial, is needed to further evaluate this important issue.

Overall, the results from long-term follow-up of KEYNOTE-010 confirm

Fig. 3. Outcomes of Patients Who Received Second-Course Treatment



that pembrolizumab monotherapy is a safe and effective agent for patients with previously treated PD-L1-expressing NSCLC, with a clear advantage over chemotherapy in both survival and tolerability. Durable long-term freedom from progression is being observed in a sizable minority of patients. ♦

About the Authors: Dr. Collier is a hematology/oncology fellow, Yale School of Medicine and Smilow Cancer Hospital. Dr. Herbst is Ensign Professor of Medicine (Medical Oncology) and professor of Pharmacology; chief of Medical Oncology, Yale Cancer Center and Smilow Cancer Hospital; associate director for Translational Research, Yale Cancer Center; and interim director of Yale Center for Immuno-

oncology, Yale Cancer Center. Dr. Goldberg is assistant professor of Medicine (Medical Oncology) at Yale Cancer Center and Smilow Cancer Hospital.

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K-LUCAS

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thoracic surgeons regarding the potential radiation hazard and morbidity of unnecessary medical or surgical procedures that would follow increased screenings. Finally, it is perceived by the general population and some politicians that screening that targets the population of current heavy smokers with more than 30 pack-years of smoking history is too narrow. Recently, the lung cancer incidence in never-smokers has been increasing rapidly and has become a hot social issue in Korea. Many individuals have insisted that these screenings should be expanded to never-smokers as well. However, there is no evidence of the effectiveness of lung cancer screening for never-smokers, so far. Moreover, the Korean NHIS and the Korean medical arena, in general, do not have the capacity to expand screening to never or light smokers at this time.

Ho Chang, a patient with lung cancer, said, "I personally welcome and am very

As a result of my long smoking history, I developed lung cancer and have been treated as a patient for more than 5 years and 5 months. If I had been able to benefit from a program like K-LUCAS in the past, I think I would have hastened my decision to stop smoking; as a result, I could have minimized the risk exposure and the chances of getting lung cancer.

—Ho Chang, Patient with Lung Cancer

much pleased with the expansion of the K-LUCAS program as a long-term smoker with more than 30 packs of cigarettes a year. As a result of my long smoking history, I developed lung cancer and have been treated as a patient for more than 5 years and 5 months. If I had been able to benefit from a program like K-LUCAS in the past, I think I would have hastened my decision to stop smoking; as a result, I could have minimized the risk exposure and the chances of getting lung cancer. I hope that this national lung cancer screening program is implemented well and that

the number of deaths from lung cancer in Korea can be lowered."

As principal investigator of K-LUCAS, I hope that the introduction of this lung cancer screening program can reduce lung cancer mortality in Korea and also provide an opportunity for participants to think about their health seriously, including quitting smoking. ♦

About the Authors: Dr. Kim is a board-certified family physician at the Center for Cancer Prevention and Detection and the Smoking Cessation Clinic, Hospital, National Cancer Center. Dr. Kim is the principal investigator of K-LUCAS. Dr. Lee is with the Division of

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EVOLVING STANDARDS OF CARE

An Interview with Dr. Mark Socinski : Tackling TKI-Refractory Disease in Patients with Oncogenic Drivers



Mark A. Socinski, MD, executive medical director of AdventHealth Cancer Institute, spoke with the *IASLC Lung Cancer News* about his personal recommendations for TKI-refractory disease, especially for patients with *EGFR* mutations. He discussed the latest IMpower150 data,¹ as well as the U.S. Food and Drug Administration's (FDA's) decision not to approve this regimen for patients with *EGFR/ALK* mutations. Dr. Socinski also shared his thoughts on the use of bevacizumab and toxicities related to a four-drug regimen.

Q: How do you typically treat patients with oncogenic drivers and TKI-refractory disease?

A: Let's start with the basics. Every patient, particularly those with adenocarcinoma, should be comprehensively tested for oncogenic drivers. The current National Comprehensive Cancer Network recommendations call out the big four: *EGFR*, *ALK*, *ROS-1*, and *BRAF*, but there are others such as *MET*, *RET*, and *HER2*. I endorse comprehensive testing for oncogenic drivers because I think that we have repeatedly seen that if an oncogenic driver is identified and the patient receives an effective targeted agent, typically a TKI, the progression-free survival (PFS) and the response rate are so much better when compared with standard chemotherapy. This is typically not a group of patients that has as "big of a bang" with immunotherapies, so all TKI options should be exhausted before considering other agents.

Specifically regarding *EGFR*, the standard of care is osimertinib in the first-line setting. We do not understand as much as we would like about why patients become refractory to osimertinib, so most of those patients, particularly in routine practice, are going to move to standard chemotherapy after disease progression. These patients almost always have adenocarcinoma, and most of these patients have good performance statuses and are chemotherapy naive; for these reasons, I



Dr. Mark A. Socinski

typically treat with a platinum-based chemotherapy doublet. I typically use carboplatin, although cisplatin would be fine. I pair it most typically with pemetrexed, although paclitaxel is an option.

Q: Do angiogenesis inhibitors have a role in this setting?

A: I believe that antiangiogenic therapy does have a role in this setting, but I will also say that not every patient is a preferred candidate for a drug like bevacizumab. In fact, administration of an antiangiogenic therapy is only appropriate in approximately 30% to 50% of patients with oncogenic drivers. If the patient is a candidate, however, I consider adding bevacizumab to the chemotherapy doublet.

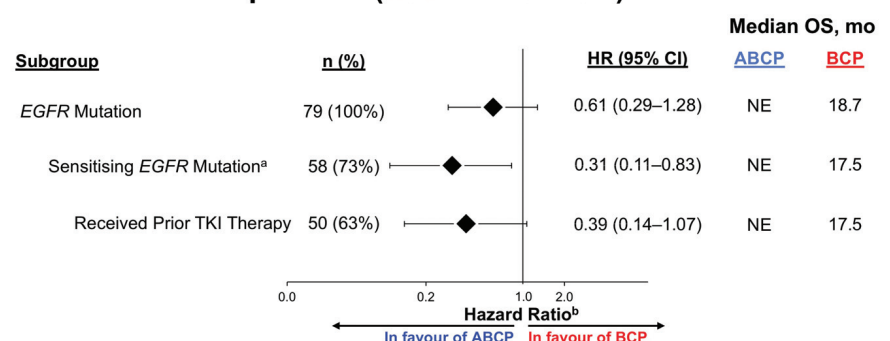
Depending on patient preferences regarding side effects, I will use either pemetrexed or paclitaxel. The POINT-BREAK trial taught us that whether pemetrexed or paclitaxel is used, the overall survival (OS) and response rates are the same.² There was a statistically significant but not clinically meaningful difference in PFS in the trial, so I think that you could use either carboplatin and pemetrexed plus bevacizumab or carboplatin and paclitaxel plus bevacizumab; the latter is the ECOG4599 regimen.³

Q: The FDA recently failed to approve the IMpower150 regimen for patients with TKI-refractory disease with *EGFR/ALK* mutations. Was this a mistake?

A: IMpower150 was performed because preclinical data suggested that the combination of a vascular endothelial growth factor (VEGF) inhibitor with a PD-1/PD-L1 inhibitor could have added synergistic effects regarding manipulation of the immune environment. For example, high VEGF states are known to be immunosuppressive in a number of different ways. If you inhibit both VEGF and PD-1/PD-L1, there might be a greater benefit, which was what IMpower150 showed, with four drugs proving superior to three drugs for the intent-to-treat population. In my mind, this validates the concept of adding immunotherapy to anti-VEGF therapy. There are a few settings in which VEGF may be a bit more involved in the pathogenesis of the disease, such as patients with *EGFR* mutations or with liver metastases. Those are the two subsets that we opted to study,

A TOTAL OF 1,202 PATIENTS with recurrent or metastatic nonsquamous NSCLC of any PD-L1/IHC status who had tumor tissue available for testing were included in IMpower150. All patients were randomly assigned 1:1:1 to one of three arms: atezolizumab/carboplatin/paclitaxel followed by atezolizumab, atezolizumab/carboplatin/paclitaxel + bevacizumab followed by atezolizumab/bevacizumab, or carboplatin/paclitaxel/bevacizumab followed by bevacizumab. All patients received 4-6 cycles of study drug. Patients received atezolizumab until disease progression or loss of clinical benefit; patients received bevacizumab until disease progression. No crossover was permitted during maintenance therapy.

OS in *EGFR*-mt patients (Arm B vs Arm C)

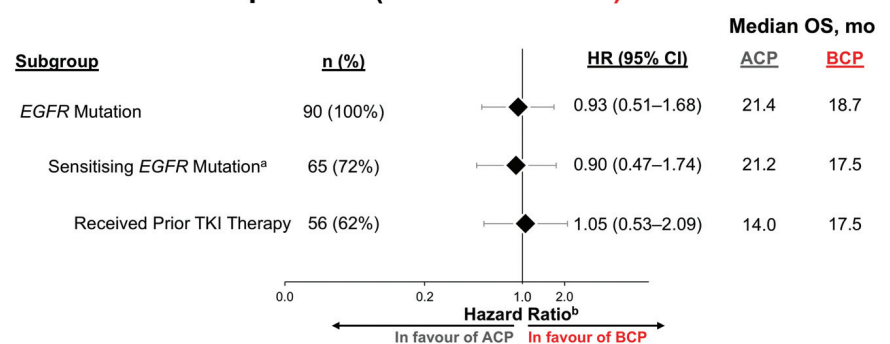


• The addition of atezolizumab to bevacizumab and chemotherapy increased OS benefit across all *EGFR* patient subgroups

NE, not estimable.
^a Defined as exon 19 deletions or L858R mutations. ^b Unstratified HR.
Data cutoff 22 Jan 2018.

Mok et al. IMpower150 in *EGFR*-mt pts
<https://bit.ly/2OD9hLE>

OS in *EGFR*-mt patients (Arm A vs Arm C)



^a Defined as exon 19 deletions or L858R mutations. ^b Unstratified HR.
Data cutoff 22 Jan 2018.

Mok et al. IMpower150 in *EGFR*-mt pts
<https://bit.ly/2OD9hLE>

Safety *EGFR*-mt patients

Incidence	Arm A: atezo + CP (n = 44)	Arm B: atezo + bev + CP (n = 33)	Arm C (control): bev + CP (n = 44)
Median number of doses received (range)			
Atezolizumab	10 (1-43)	14 (1-38)	NA
Bevacizumab	NA	12 (1-38)	8.5 (1-38)
Treatment-related AE ^a	39 (89%)	33 (100%)	42 (96%)
Grade 3-4	25 (57%)	21 (64%)	25 (57%)
Grade 5 ^b	0 (0%)	0 (0%)	1 (2%)
Serious AE	15 (34%)	12 (36%)	9 (21%)
AE leading to withdrawal from any treatment	6 (14%)	11 (33%)	7 (16%)
Immune-related AEs^c in > 5 patients in any arm			
Rash	16 (36%)	10 (30%)	5 (11%)
Hypothyroidism	1 (2%)	6 (18%)	1 (2%)

^a Related to any study treatment. ^b Pulmonary haemorrhage. ^c Immune-related AEs were defined using MedDRA Preferred Terms that included both diagnosed immune conditions and signs and symptoms potentially representative of immune-related events, regardless of investigator-assessed causality. Data cutoff 22 Jan 2018.

Mok et al. IMpower150 in *EGFR*-mt pts
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and both showed positive effects for the addition of anti-PD-L1 therapy to anti-VEGF therapy. A substitution strategy using anti-PD-L1 for anti-VEGF ther-

apy in Arm A resulted in no significant difference—maybe a trend, but not like what was seen with the additive effect.

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SMOKING CESSATION & TOBACCO CONTROL

Can E-Cigarettes Help Patients Stop Smoking Combustible Cigarettes?

By Li-Shiun Chen, MD, MPH, ScD, and
Laura J. Bierut, MD

Combustible tobacco products, primarily cigarettes, continue to be the leading cause of cancer, and in the most recent surveys, an estimated 34.3 million adults smoke (14% of the U.S. adult population).¹ Whereas combustible cigarette usage continues to decrease, e-cigarettes have grown in popularity, and many patients who smoke ask their physician about e-cigarettes. However, evidence on the efficacy of e-cigarettes as a smoking cessation tool has been limited. The Cochrane review based on two trials suggested that

e-cigarettes may help combustible cigarette smokers quit and may aid smokers who are unable to stop smoking altogether to reduce their cigarette consumption.² However, the comparison of e-cigarettes with combination nicotine replacement therapy (NRT) (e.g., nicotine patch plus nicotine lozenges, which are more effective than the nicotine patch alone) on efficacy as a smoking cessation tool has been much needed.³

In a new trial by Hajek et al., undertaken in the United Kingdom, e-cigarettes were more effective at helping smokers quit combustible cigarettes than NRT of patients' choice, including use of combination NRT.⁴ All smokers were provided

at least four weekly counseling sessions and randomly selected to e-cigarettes or NRT for 3 months in this trial of 886 smokers attending smoking cessation services. Bio-verified abstinence from combustible cigarette use was 18% at 1 year in the e-cigarette group versus 9.9% in the NRT group. Although cessation of combustible cigarettes was significantly better in the e-cigarette group, a less positive note was that for the smokers who achieved abstinence in the e-cigarette group, most (80%) continued using e-cigarettes at 1 year. Further, approximately 40% of smokers assigned to e-cigarettes had dual use of combustible and e-cigarettes use at 1 year. More importantly, the overall success of this smoking cessation trial is only modest at best and ineffective for most.

The new study aligns with the 2018 American Cancer Society Position Statement on Electronic Cigarettes. It recommends that clinicians support all attempts to quit combustible tobacco use, no matter what approach patients use. To help smokers quit, clinicians should advise patients to use U.S. Food and Drug Administration–approved cessation aids and should work with smokers to eventually stop using all tobacco products, including e-cigarettes.⁵ Some smokers, despite advice and assistance, will continue to smoke cigarettes. These individuals should be encouraged to switch to the least harmful tobacco product, and switching to e-cigarettes is preferable to continued smoking of combustible cigarettes. The preponderance of scientific evidence supports that current e-cigarettes products are demonstrably less harmful than combustible cigarettes.⁶

E-Cigarettes and Public Health
Combustible and e-cigarettes' effects on public health continue to rapidly evolve. For combustible cigarette smokers, e-cigarettes represent a reasonable



opportunity to successfully quit combustible cigarette smoking and reduce smoking-related illnesses. For non-smoking adolescents and young adults, initiation of e-cigarettes represents a potential health concern. There is a rapidly increasing prevalence of e-cigarette use and “vaping” among youth in the United States.^{7,8} The net public health outcome of e-cigarettes will depend on the balance between decreasing combustible cigarette use in adults while limiting youth initiation of smoking. The current trend shows that combustible cigarette smoking continues to decrease in youth and young adults even while vaping is on the rise,⁹ and it is hoped that e-cigarettes will contribute to a positive public health balance. ♦

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INDUSTRY AND REGULATORY NEWS

Pembrolizumab Receives Third-Line Approval for Metastatic SCLC

June 17, 2019—Pembrolizumab received accelerated approval from the U.S. Food and Drug Administration for treatment of patients with metastatic SCLC with disease progression during or after platinum-based chemotherapy and at least one other line of therapy.

Approval was based on results from KEYNOTE-158 and KEYNOTE-028. A total of 83 patients received either 200 mg of IV pembrolizumab every 3 weeks (64 patients), which was found to be the recommended dosage, or 10 mg/kg IV every 2 weeks (19 patients). Treatment continued for a maximum of 24 months or until disease progression or unacceptable toxicity.

The ORR was 19% (95% CI: 11-29), and the CR rate was 2%. For the 16 patients who demonstrated a response, the percentage with durable responses at 6, 12 or more, and 18 or more months were 94%, 63%, and 56%, respectively. Study treatment was discontinued due to adverse events (AEs) in 9% of patients; 25% had at least one dose withheld due to an AE. Common AEs were fatigue, decreased appetite, cough, nausea, and constipation, each of which occurred in at least 20% of patients. Serious AEs occurred in 31% of patients, with pneumonia and pleural effusion being the most frequent (> 2%).

Pembrolizumab was granted orphan drug designation for SCLC in October 2017. ♦

TKI-Refractory Disease

from page 21

Patients with *EGFR/ALK* mutations have been excluded from enrollment in every trial presented to date, with the exception of IMpower150 and IMpower130, which assumed that patients had received prior TKI therapy if appropriate. (Not every patient with an *EGFR* mutation has a sensitizing mutation, so there are patients with *EGFR* mutations for whom TKI therapy was not appropriate.) Going into IMpower150, we had no way to know how many patients would end up on the trial. Regarding patients with *EGFR* mutations, there were ultimately 45 on Arm A, 34 on Arm B, and 45 on Arm C. Although the study regimen included this population, the FDA was not sold on the benefit for the *EGFR*-mutation population because of the small numbers. I have been told that there were no other issues preventing approval for this group other than the inability to have prospectively powered the trial specifically for patients with *EGFR* mutations, which was not possible because we did not know beforehand how many patients with *EGFR* or *ALK* mutations would end up on the trial and how many of those patients had “failed” prior TKI therapy.

Regarding IMpower150 OS data presented at the European Society for Medical Oncology in November 2018, the hazard ratio for OS for patients with *EGFR*-sensitizing mutations was 0.31 for the addition of atezolizumab to the ECOG4599 regimen, which is pretty convincing. Similarly, the hazard ratio for patients with *EGFR* mutations who had received a prior TKI was 0.39. So in my mind, these hazard ratios are impressive despite the small population of patients with *EGFR* mutations in this trial.

Q: Does toxicity preempt the use of a four-drug regimen?

A: Patient selection is key. If you take all-comers with nonsquamous NSCLC, then 60% to 70% of patients would have a contraindication to bevacizumab. These patients often have untreated brain metastases, comorbidities, recent myocardial infarctions, history of stroke, and/or hypertension that’s difficult to control. However, if a patient is a perfect candidate for bevacizumab, POINT-BREAK showed acceptable toxicities for the addition of bevacizumab to carboplatin and paclitaxel or carboplatin and pemetrexed. In my experience, adding immunotherapy to chemotherapy doesn’t exacerbate the toxicities of either modality. However,

because more therapy is being given, there is going to be the risk of more toxicity. Physicians must talk to patients about the advantages and risks of being more aggressive with therapy. You have to listen to patients about preferences. Some patients will want to do whatever it takes to stabilize or shrink their disease; other patients feel differently. I personally do not think the four-drug regimen is prohibitive with regard to toxicity. Four-drug regimens have been administered before in different settings, even in settings where the four drugs did not help. Here we have a situation in which a four-drug regimen seems to help—quite significantly for patients with *EGFR* mutations, which is, I think, the only oncogenic driver that we can talk about somewhat confidently. The *ALK* population in IMpower150 was too small, and we do not have data regarding other drivers such as *BRAF* and *MET*. I think many people might draw conclusions about these other drivers, but these conclusions would not be data-driven.

Q: Do you continue the TKI during chemotherapy if the patient has been shown to have TKI-refractory disease?

A: When the decision is made that the TKI has worn out its welcome and it is time to move on to chemotherapy—whether it is chemotherapy alone or chemotherapy with bevacizumab or the IMpower150 regimen—then I stop the TKI. Based on the IMPRESS data and other trials, I do not believe that keeping the TKI has a benefit.⁴ Again, the more drugs you have, the higher the risk of toxicity. Although it might be safe, I am not sure that I am providing a greater benefit by continuing the TKI. There is room for discussion, however, about whether the TKI could or should be done as maintenance therapy as part of the initial post-TKI regimen. ♦

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LETTER TO THE EDITOR

Opening Trial to Patients Living with HIV

In response to the article by Dr. Jarushka Naidoo in the April issue, it should be noted that it remains an open question as to whether it is safe to administer immune checkpoint inhibitors (ICI) to people living with HIV (PLWHIV) who have cancer because they have been usually excluded from clinical trials; however, these patients are at greater risk of developing cancer.

Several retrospective series showed anti-PD-1 therapy appears to be safe, and in some cases, very effective in PLWHIV with cancer. There was no unexpected toxicity and no increase in HIV viral load. No immune reconstitution inflammatory syndrome (IRIS) or opportunistic infections were identified while on treatment.¹⁻⁵ Additional research must address several unanswered questions regarding the use of ICI in PLWHIV with cancer. For example, characterization of PD-L1 expression and tumor mutational burden is lacking in NSCLC. The overall response rate and the response duration to ICI, as well as factors that might affect response to ICI, are unknown. Prospective studies are needed. Several ongoing clinical trials are evaluating ICIs in PLWHIV without cancer (NCT03367754, NCT03239899) and in PLWHIV with advanced cancer (nivolumab alone or in combination with ipilimumab, NCT02408861; pembrolizumab NCT02595866). Furthermore, a phase II study by the Spanish Lung Cancer Group is evaluating durvalumab in solid tumors (NCT03094286), and an ongoing French phase II study is evaluating nivolumab for PLWHIV with NSCLC (NCT03304093). Finally, the effects of ICIs on HIV-specific immune response and HIV reservoirs warrants further investigation in prospective studies. ♦

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This is an investigational trial. TTFields has not been approved by the US FDA for treatment of NSCLC.

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